Polyketide Assembly by Alkene-Alkyne Reductive Cross-Coupling: Spiroketals Through the Union of Homoallylic Alcohols

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Supporting Information

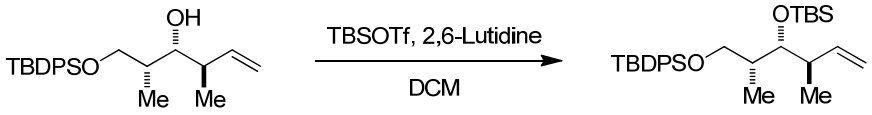
General Information: ^{1}H NMR data were recorded at 400 MHz on a Bruker AM-400, and ^{13}C NMR data were recorded at 100 MHz on a Bruker AM-400 standardized to residual chloroform (7.26 ppm for ^{1}H and 77.36 ppm for ^{13}C). Infrared spectra were acquired on a PerkenElmer SpectrumOne FT-IR instrument, optical rotations were acquired on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. HRMS data were obtained at the University of Illinois at Urbana-Champagne Mass Spectrometry Lab.

Diethyl ether, tetrahydrofuran, toluene and dichloromethane were dried over activated alumina columns and sparged with argon prior to use. Ti(O*i*-Pr)$_4$ (Aldrich, 97%) was distilled prior to use (70 ˚C, 1 Torr). Butyllithium and *c*-C_5H_9MgCl (Aldrich) were titrated by the method of Love *et al*.[1] Trimethylamine N-oxide-dihydrate (Acros) was purified according to Frazen[2] and stored/handled in a glove box. 9-BBN dimer (Alfa Aesar) was used as received and stored in a dessicator at room temperature. (+)/(-)-Ipc$_2$BOMe was purchased from Aldrich and stored/handled in a glove box.

All reactions were conducted in flame-dried glass flasks under an argon atmosphere unless otherwise indicated. Flash column chromatography was performed using Silacycle SilaFlash P60 silica gel, 40-63 μm particle size, preparative TLC was performed using Analtech Uniplate 1000μm silica plates, and TLC was performed using EMD Chemicals Inc. TLC Silica Gel 60 F_{254} glass plates with the aid of uv fluorescence, KM_nO_4, or *p*-anisaldehyde for visualization.

Compounds **10**,[3] **12**,[4] **16**,[5] **22**,[6] **23**,[7] and **29**[8] were all prepared according to previous reports. The stereochemistry of asymmetric crotylation/allylation by chiral boron reagents are based on Brown's transition state models.[9] Enantiomeric excess was assumed to be high (> 90 %) based on analogous crotylations, and was confirmed by the presence of one diastereomer (based on ^{1}H NMR analysis) after the Ti-mediated reductive coupling of two chiral coupling partners. The stereochemistry of asymmetric propargylations was based on Marshall's transition state models.[10] The stereochemistry of spiroketals **35**-**38** were assigned based on the expected preference for the thermodynamically preferred doubly anomeric spiroketal;[11] all ^{1}H NMR coupling constants and ^{1}H cosy spectral data are consistent with this assignment.

Experimental Data:

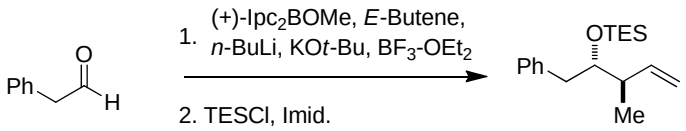


14

(5*R*,6*R*)-5-((*R*)-but-3-en-2-yl)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (14):
Olefin **14** was prepared by standard TBS-protection of the known homoallylic alcohol[12] using TBSOTf.[13]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 4H), 7.49 – 7.32 (m, 6H), 5.94 – 5.72 (m, 1H), 5.02 – 4.87 (m, 2H), 3.81 (dd, *J* = 4.8, 3.4 Hz, 1H), 3.60 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.48 (dd, *J* = 9.9, 6.6 Hz, 1H), 2.37 (dd, *J* = 12.7, 6.8 Hz, 1H), 1.87 (ddd, *J* = 13.6, 6.8, 3.4 Hz, 1H), 1.11 (s, 9H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.97 – 0.84 (m, 12H), 0.09 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.2, 136.0, 135.9, 134.4, 134.3, 129.8, 129.8, 127.9, 114.3, 75.6, 67.2, 43.4, 39.4, 27.2, 26.5, 19.6, 18.7, 17.3, 12.3, -3.3, -3.6; **IR** (neat) cm^{-1} 3051, 2958, 2929, 2857, 1472, 1462, 1427, 1251, 1110, 1050, 1005, 906, 834, 734, 700; **LRMS** (ESI) Calculated for $C_{24}H_{35}O_2Si$ [(M+1) – TES] 282.2, found 282.2; $[\alpha]_D^{20}$ = -3.8° (*c* = 3.15 mg/mL, $CHCl_3$).

18

(((2*R*,3*R*)-1-(benzyloxy)-3-methylpent-4-en-2-yl)oxy)(tert-butyl)dimethylsilane (18):
Olefin **18** was prepared by standard TBS-protection of the known homoallylic alcohol[14] using TBSCl[15].
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.91 – 5.72 (m, 1H), 5.01 (dd, *J* = 10.3, 6.4 Hz, 2H), 4.53 – 4.35 (m, 2H), 3.76 (td, *J* = 5.7, 3.4 Hz, 1H), 3.38 (qd, *J* = 9.5, 5.8 Hz, 2H), 2.49 – 2.32 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 7.1 Hz, 6H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.4, 138.8, 128.6, 127.9, 127.8, 115.1, 75.1, 73.6, 41.9, 26.2, 18.5, 17.3, -3.8, -4.5; **IR** (neat) cm^{-1} 2956, 2928, 2895, 2856, 1639, 1471, 1454, 1361, 1251, 1099, 1038, 912, 833, 774, 732, 695; **HRMS** (ESI) Calculated for $C_{19}H_{32}O_2SiNa$ [M+Na] 343.2069, found 343.2058; $[\alpha]_D^{20}$ = +3.63° (*c* = 1.6 mg/mL, $CHCl_3$).



20

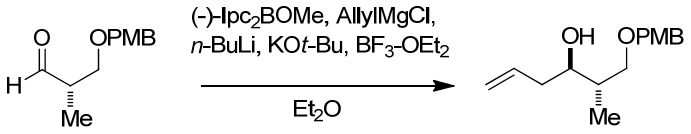
triethyl(((2*S*,3*R*)-3-methyl-1-phenylpent-4-en-2-yl)oxy)silane 20:
To a stirred solution of KO*t*-Bu (1.86 g, 16.56 mmol) in THF (20 mL) at -78 °C was cannulad *trans* butene (3.5 g, 62.5 mmol). To this was slowly added *n*-BuLi (6.64 mL (2.50M), 16.6 mmol) and the resulting solution was slowly warmed to -50 °C and the bright yellow/green solution was stirred at -50 °C for 30 minutes. After cooling to -78 °C, a solution of (+)-Ipc_2BOMe (5.25 g, 16.6 mmol) in THF (13.3 mL) was added dropwise to obtain a colorless/faint yellow solution. To this was added $BF_3{\cdot}OEt_2$ (2.81 mL, 22.38 mmol) dropwise to obtain a turbid white suspension. After the suspension was stirred at -78 °C for 10 minutes, a solution of phenylacetaldehyde (1.5 g, 12.5 mmol) in THF (6.6 mL) was added dropwise. The slurry was stirred at -78 °C for 3 hours and quenched by the addition of 15 mL 15% NaOH. The reaction flask was then fitted with a condenser, 15 mL 30% H_2O_2 was added, and the mixture was left to warm and stir overnight. Upon obtaining a colorless, biphasic solution the mixture was extracted with Et_2O (3x 50 mL), the organic layer was washed with brine (75 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography (700 mL of silica) eluting with a gradient of 500 mL each of 1% → 2% → 3% → 4% → 5% EtOAc/hexanes to obtain a light yellow oil.

Data for the Homoallylic alcohol, 20a:
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.8, 6.9 Hz, 2H), 7.29 – 7.17 (m, 3H), 5.89 (ddd, *J* = 17.1, 10.5, 8.0 Hz, 1H), 5.16 (dddd, *J* = 17.1, 13.0, 1.9, 1.0 Hz, 2H), 3.69 (td, *J* = 8.9, 3.9 Hz, 1H), 2.86 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.65 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.41 – 2.24 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.2, 139.2, 129.6, 128.7, 126.5, 116.3, 76.0, 43.5, 41.1, 21.2, 16.6; **IR** (neat) cm^{-1} 3420, 3064, 3027, 2963, 2929, 1638, 1603, 1494, 1454, 1420, 1031, 998, 912, 743, 699; **HRMS** (ESI) Calculated for $C_{12}H_{16}ONa$ [M+Na] 199.1099, found 199.1095. $[\alpha]_D^{20}$ = -18.1 (*c* = 7.43 mg/mL, $CHCl_3$).

TES-protection using standard conditions with TESCl[16] provided the desired material as a yellow oil in 61% yield over the two steps.

Data for TES-protected, 20:

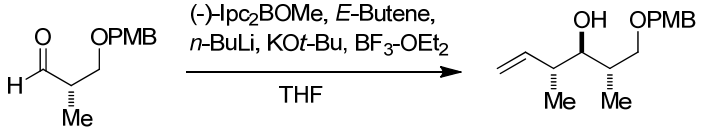
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.01 (m, 5H), 6.01 – 5.76 (m, 1H), 5.17 – 4.93 (m, 2H), 3.83 (ddd, *J* = 7.3, 6.0, 3.1 Hz, 1H), 2.71 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.63 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.34 – 2.19 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.88 (dd, *J* = 9.5, 6.3 Hz, 9H), 0.46 (ddd, *J* = 16.3, 8.0, 2.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 140.0, 129.9, 128.4, 126.2, 115.3, 77.8, 43.1, 40.9, 16.1, 7.2, 5.3; **IR** (neat) cm^{-1} 2954, 2925, 2876, 1457, 1417, 1260, 1241, 1085, 1047, 1015, 914, 770, 738; **LRMS** (ESI) Calculated for $C_{12}H_{16}OSi$ [(M+1) – TES] 177.1, found 177.1; $[\alpha]_D^{20}$ = -3.6° (*c* = 1.65 mg/mL, $CHCl_3$).



25a **25**

(2S,3*R*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-ol (25): Asymmetric allylation of aldehyde 25a according to the procedure of Brown *et al*.[17] provided anti-alcohol **25**, 0.150 g, 50 %, as a yellow oil.

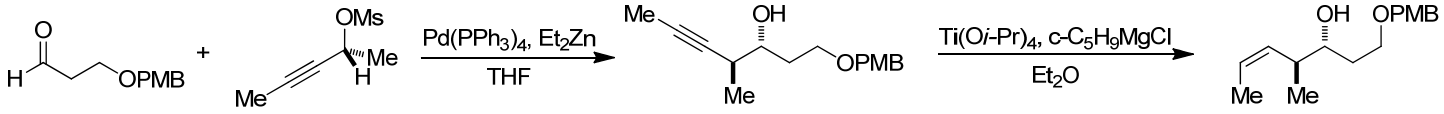
$[\alpha]_D^{20}$ = -5.8° (*c* = 1.45 mg/mL, $CHCl_3$). All remaining spectral data were consistent with the known enantiomer.



25a **27**

(2S,3*R*,4*R*)-1-((4-methoxybenzyl)oxy)-2,4-dimethylhex-5-en-3-ol (27): Following the procedure above for homoallylic alcohol **20**, alcohol **27** was obtained as a yellow oil (0.311 g, 62 %).

$[\alpha]_D^{20}$ = -3.7° (*c* = 3.2 mg/mL, $CHCl_3$). All remaining spectral data were consistent with the known enantiomer.[18]



31a **31**

The PMB-protected aldehyde [19] was propargylated using (*R*)-pent-3-yn-2-yl methanesulfonate[20] according to the method of Marshal et. al.[21] to give 0.722 g, 36% of **(3*R*,4*S*)-1-((4-methoxybenzyl)oxy)-4-methylhept-5-yn-3-ol (31a)** as a yellow oil.

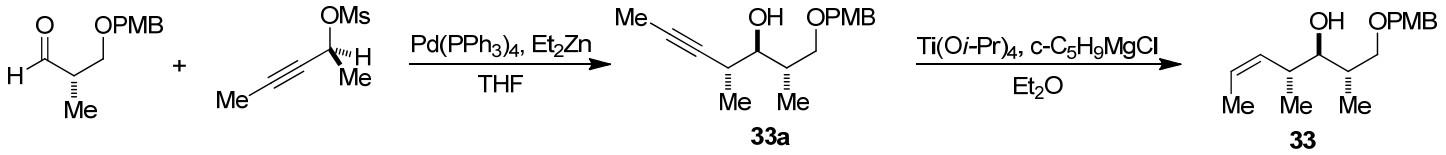
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.73 – 3.50 (m, 3H), 2.64 (d, *J* = 4.8 Hz, 1H), 2.56 – 2.41 (m, 1H), 1.86 – 1.74 (m, 5H), 1.17 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.54, 130.53, 129.63, 114.13, 80.28, 78.52, 73.55, 73.24, 68.62, 55.58, 34.68, 33.36, 17.58, 3.89; **IR** (neat) cm^{-1} 3469, 2919, 2861, 1613, 1586, 1514, 1455, 1364, 1302, 1248, 1173, 1091, 1035, 821; **HRMS** (ESI) Calculated for $C_{16}H_{23}O_3$ [M+1] 263.1647, found 263.1635; $[\alpha]_D^{20}$ = +2.0° (*c* = 2.5 mg/mL, $CHCl_3$).

(3*R*,4*S*,*Z*)-1-((4-methoxybenzyl)oxy)-4-methylhept-5-en-3-ol (31):

Alkyne 31a (0.10 g, 0.38 mmol) was dissolved in Et_2O (3.8 mL) and Ti(O*i*-Pr)$_4$ (0.461 mL, 1.519 mmol) was added at rt. The colorless solution was cooled to -78 °C and c-C_5H_9MgCl (1.9M/Et_2O, 1.60 mL, 3.04 mmol) was added dropwise. The bright yellow solution was slowly warmed to -30 °C and stirred for about 1 hr, then quenched by the addition of 1M HCl (5 mL) and the mixture was warmed to rt and stirred until a transparent, biphasic mixture was obtained (about 20 minutes). The mixture was extracted with Et_2O (3 x 10 mL), the organic phase was washed with brine, dried over $MgSO_4$ and concentrated to give a yellow oil. Column chromatography (7:1 hexanes:EtOAc) provided 0.077 g, 77% of the desired olefin as a yellow oil.

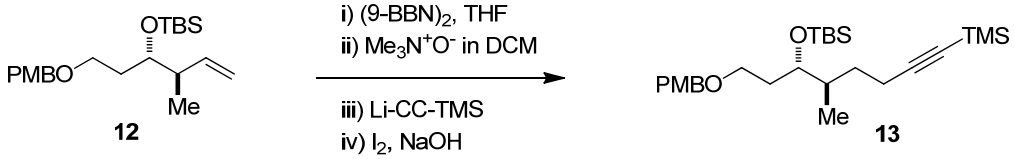
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.63 – 5.48 (m, 1H), 5.36 – 5.23 (m, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.73 – 3.52 (m, 3H), 2.68 (d, *J* = 2.0 Hz, 1H), 2.61 – 2.43 (m, 1H), 1.79 – 1.67 (m, 2H), 1.63 (dd, *J* = 6.8, 1.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 132.9, 130.5, 129.6, 125.5, 114.1, 74.9, 73.3, 69.1,

55.6, 37.8, 34.0, 17.1, 13.5; **IR** (neat) cm^{-1} 3447, 2959, 2925, 2857, 1712, 1612, 1513, 1462, 1372, 1302, 1249, 1171, 1097, 1035, 822, 754; **HRMS** (ESI) Calculated for $C_{16}H_{25}O_3$ [M+1] 265.1804, found 265.1801; $[\alpha]_D^{20}$ = -5.4° (*c* = 1.85, $CHCl_3$).

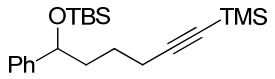


(2*S*,3*R*,4*R*,*Z*)-1-((4-methoxybenzyl)oxy)-2,4-dimethylhept-5-en-3-ol (33):
Olefin **33** was prepared as olefin **31** using aldehyde **25a** and (*S*)-pent-3-yn-2-yl methanesulfonate. The resulting alkyne **33a** was used directly in the reduction to provide **33** (0.205 g, 51 %) as a light yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.48 (dd, *J* = 6.5, 4.3 Hz, 2H), 4.43 (s, 2H), 3.53 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.47 (dd, *J* = 9.1, 7.6 Hz, 1H), 3.40 (d, *J* = 2.5 Hz, 1H), 3.36 (dd, *J* = 7.4, 3.9 Hz, 1H), 2.72 – 2.54 (m, 1H), 1.92 – 1.79 (m, 1H), 1.65 – 1.58 (m, 3H), 1.05 – 0.99 (m, 4H), 0.84 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.56, 131.95, 130.20, 129.60, 124.30, 114.11, 80.41, 75.33, 73.38, 55.50, 36.50, 34.75, 18.24, 13.32; **IR** (neat) cm^{-1} 3478, 2959, 2930, 2870, 1612, 1586, 1512, 1458, 1301, 1246, 1173, 1082, 1034, 985, 820, 734; **HRMS** (ESI) Calculated for $C_{17}H_{26}O_3Na$ [M+Na] 301.1780, found 301.1779; $[\alpha]_D^{20}$ =+4.24° (*c* = 1.65 mg/mL, $CHCl_3$).

Representative procedure for the formal hydroalkynylation of homoallyl ethers:



***tert*-butyl(((3S,4*R*)-1-((4-methoxybenzyl)oxy)-4-methyl-8-(trimethylsilyl)oct-7-yn-3-yl)oxy)dimethylsilane (13):**
A 10 mL roundbottom flasked was charged with 9-BBN dimer (0.058 g, 0.236 mmol) and purged with Ar. To this was added a solution of olefin **12** (0.166 g, 0.454 mmol) in THF (1.0 mL) at rt. This was allowed to stir at rt until the disappearance of olefin was comfirmed by TLC (about 2.5 hr). The resulting solution was colled to 0 °C and a solution of TMANO (0.036 g, 0.477 mmol) in DCM (0.5 mL) was added slowly. The ice bath was removed and the mixture was stirred at rt for 30 minutes. In a separate flask the acetylide was prepared by dropwise addition of *n*-BuLi (0.272 mL 2.5 M/hexanes, 0.681 mmol) to TMS-acetylene (0.096 mL, 0.681 mmol) in THF (1.7 mL) at -78 °C. The acetylide formation was stirred at -78 °C for 45 minutes, then added via syringe to the borinate solution, which has been cooled to 0 °C. The ice bath was removed and the resulting solution was warmed to rt. After stirring at rt for 45 minutes, the yellow solution was cooled to -78 °C and a solution of I_2 (0.161 g, 0.636 mmol) in THF (2.8 mL) was added dropwise. The resulting red/orange solution was stirred at -78 for an additional 20 minutes at which time a rust red/orange slurry was obtained and 2 mL NaOH (1M) was added followed by 0.7 mL H_2O_2 (30%). The bath was removed and the mixture was warmed to rt then diluted with H_2O/DCM (20 mL 1:1). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (1% → 3% EtOAc/hexanes) provided the desired product (0.181 g, 86%) as a light yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.41 (m, 2H), 3.80 (s, 3H), 3.76-3.72 (m, 1H), 3.57-3.52 (m, 2H), 2.29-2.16 (m, 2H), 1.78 (m, 1H), 1.65 (m, 1H), 1.54 (m, 2H), 1.29 (m, 1H), .88 (m, 12H), 0.14 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 131.0, 129.5, 114.0, 107.6, 84.7, 72.9, 72.6, 67.6, 55.5, 37.8, 32.2, 31.8, 26.2, 18.4, 18.2, 13.8, 0.5, -3.9, -4.3; **IR** (neat) cm^{-1} 2957, 2857, 2174, 1614, 1587, 1514, 1463, 1360, 1255, 1099, 1040, 839; **HRMS** (ESI) Calculated for $C_{26}H_{47}O_3Si_2$ [M+1] 463.3064, found 463.3051; $[\alpha]_D^{20}$ = -14.8° (*c* = 2.15 mg/mL, $CHCl_3$).



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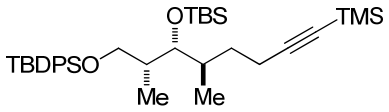
***tert*-butyldimethyl((1-phenyl-6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (11)**: Obtained 0.069 g, 84% as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.22-7.02 (m, 1H), 4.68 (t, J = 6.4 Hz, 1H), 2.20 (td, J = 3.2 Hz, J = 7.2 Hz, 2H), 1.82-1.75 (m, 2H), 1.54-1.48 (m, 2H), 0.89 (s, 9H), 0.13 (s, 9H), 0.03 (s, 3H), -0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.7, 128.3, 127.1, 126.1, 107.6, 84.9, 74.7, 40.0, 26.2, 24.6, 20.0, 18.5, 0.5, -4.3, -4.6; **IR** (neat) cm^{-1} 2955, 2929, 2857, 2174, 1471, 1361, 1249, 1093, 834, 774, 698; **HRMS** (ESI) Calculated for $C_{21}H_{37}OSi_2$ [M+1] 361.2383, found 361.2371.



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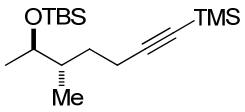
(5*R*,6*R*)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-5-((R)-6-(trimethylsilyl)hex-5-yn-2-yl)-4,8-dioxa-3,9-disilaundecane (15): Obtained 0.274 g, 74% as a yellow oil.

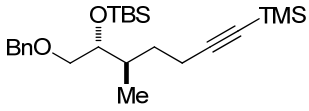
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (M, 4h), 7.40-7.37 (m, 6H), 3.76 (m, 1H), 3.49 (m, 1H), 3.41 (m, 1H), 2.29-2.26 (m, 1H), 2.18-2.14 (m, 1H), 1.81-1.63 (m, 3H), 1.27-1.24 (m, 1H), 1.06 (s, 9H), 0.88-0.86 (m, 12H), 0.80 (d, J = 6.8 Hz), 0.13 (s, 9 H), 0.55 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.9, 134.3, 134.2, 129.8, 127.9, 107.9, 84.7, 74.6, 67.6, 38.2, 37.9, 32.4, 27.2, 26.4, 19.5, 18.7, 18.3, 15.7, 11.8, 0.5, -3.5, -3.9; **IR** (neat) cm^{-1} 2957, 2930, 2857, 2175, 1472, 1428, 1250, 1111, 838, 701; **HRMS** (ESI) Calculated for $C_{35}H_{59}O_2Si_3$ [M+1] 595.3823, found 595.3832; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ = -15.5° (*c* = 1.80 mg/mL, $CHCl_3$).



17

***tert*-butyldimethyl(((2*R*,3*S*)-3-methyl-7-(trimethylsilyl)hept-6-yn-2-yl)oxy)silane (17):** Obtained 0.632 g, 86% as a light yellow oil.

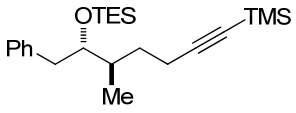
^{1}H NMR (400 MHz, $CDCl_3$); δ 3.69 (m, 1H), 2.32-2.20 (m, 1H), 2.18-2.12 (m, 1H), 1.64-1.59 (m, 1H), 2.27-1.30 (m, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.14 (s, 9H), 0.04 (d, *J* = 1.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.9, 84.5, 71.9, 39.6, 31.7, 26.2, 19.7, 18.4, 18.2, 14.5, 0.5, -4.0, -4.4; **IR** (neat, cm-1) 2957, 2929, 2857, 2175, 1472, 1462, 1249, 1101, 1040, 853, 773; **HRMS** (ESI) Calculated for $C_{17}H_{37}OSi_2$ [M+1] 313.2383, found 313.2372; $[\propto]_{\mathrm{D}}^{20}$ = -12.0° (*c* = 2.00 mg/mL, $CHCl_3$).



19

(((2*R*,3*R*)-1-(benzyloxy)-3-methyl-7-(trimethylsilyl)hept-6-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (19): Obtained 0.376 g, 72% as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.35-7.25 (m, 5H), 4.25 (m, 2H), 3.77 (m, 1H), 3.5-3.46 (m, 1H), 3.43-3.39 (m, 1H), 2.32-2.28 (m, 1H), 2.23-2.16 (m, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.38 (m, 1H), 0.93-0.87 (m, 12H), 0.16 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$); δ 138.7, 128.6, 127.8, 127.7, 107.9, 84.6, 75.5, 73.6, 73.1, 36.3, 30.7, 26.2, 18.5, 18.2, 15.6, 0.5, -3.9, -4.5. **IR** (neat, cm-1); 3031, 2956, 2929, 2857, 2174, 1471, 1455, 1361, 1249, 1100, 1039, 839. **HRMS** (ESI) Calculated for $C_{24}H_{43}O_2Si_2$ [M+1] 419.2802, found 419.2800; $[\propto]_{\mathrm{D}}^{20}$ = +3.4° (*c* = 1.45 mg/mL, $CHCl_3$).

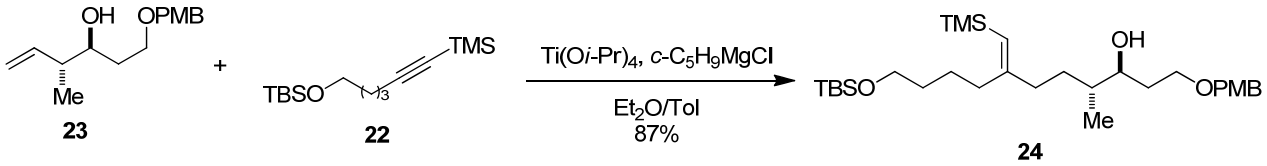


21

triethyl((2*S*,3*R*)-3-methyl-1-phenyl-7-(trimethylsilyl)hept-6-yn-2-yl)silane (21): Obtained 0.039 g, 78 % as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.28-7.7.20 (m, 5H), 3.80 (m, 1H), 2.70 (m, 1H), 2.61 (m, 1H), 2.35 (m, 1H), 2.24 (m, 1H), 1.81-1.67 (m, 2H), 1.43 (m, 1H), 0.96 (d, J = 6.8 Hz 3H), 0.85 (t, J = 8 Hz 9H), 0.42 (m, 6H), 0.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 140.3, 129.9, 128.4, 126.2, 107.6, 84.8, 77.9, 39.5, 37.8, 31.5, 18.3, 14.5, 7.2, 5.2, 0.4; **IR** (neat, cm^{-1}) 3028, 2956, 2876, 2174, 1603, 1456, 1249, 1083, 1005, 842, 739; **HRMS** (ESI) Calculated for $C_{17}H_{26}ONa$ [(M+Na)-TES] 297.2, found 297.2; $[\propto]_D^{20}$ = -6.5° (*c* = 3.35 mg/mL, $CHCl_3$).

Representative procedure for the Ti-alkoxide-mediated reductive cross coupling to generate vinyl silanes:

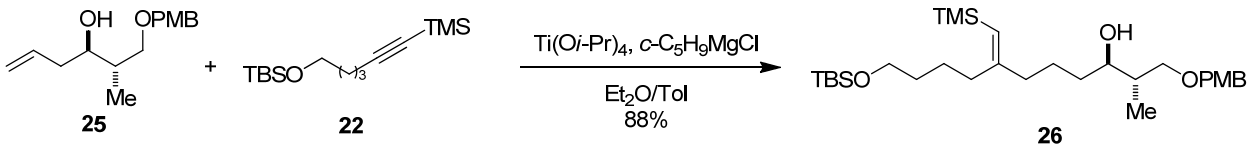


23 **22** **24**

(3*S*,4*R*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-methyl-7-((trimethylsilyl)methylene)undecan-3-ol (24): This procedure is the higher yielding of two runs.

Ti(O*i*-Pr)$_4$ (0.061 mL, 0.20 mmol) was added to a solution of alkyne **22** (0.057 g, 0.2 mmol) in toluene (1.6 mL) at rt. The colorless solution was cooled to -78 °C and *c*-C_5H_9MgCl (1.9 M/Et2O, 0.210 mL, 0.40 mmol) was added dropwise to generate a bright yellow solution. The resulting solution was allowed to slowly warm to -30°C over an hour (a brown solution was obtained in this time), and stirred at -30 °C for 2 hours. In a separate flask the lithium alkoxide of homoallylic alcohol **23** was generated by the addition of *n*-BuLi (2.5M/hexanes, 0.035 mL, 0.088 mmol) to alcohol **23** (0.020 g, 0.080 mmol) in Et_2O (0.8 mL) at -78 °C. The titanium complex (now a black slurry with a red hue at the solvent/Ar interface) was cooled to -78 °C, and the separate alkoxide solution was warmed to 0 °C and stirred at this temperature for 10 minutes, whereupon it was transferred dropwise via syringe to the titanium complex at -78 °C, using an additional 0.2 mL Et_2O to aid in the transfer. The resulting dark brown/black solution was allowed to slowly warm to -30 °C and stirred at this temperature for 5 hrs. Upon completion (as indicated by TLC) the reaction was quenched with 3 mL HCl (1M) and warmed to rt, and stirred until a biphasic, transparent mixture was obtained (about 30 minutes). The resulting mixture was diluted with H_2O (3 mL), extracted with EtOAc (3 x 15 mL) and the organic phase was washed with brine (15 mL), dried over $MgSO_4$ and concentrated to give a yellow oil. Column chromatography (8:1 hexane:EtOAc) provided 0.037 g, 88% of the desired vinyl silane as a yellow oil. A second run provided the desired product in 85 % isolated yield.

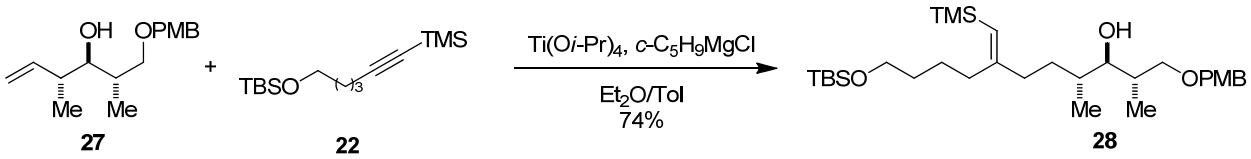
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8, 2H), 5.17 (s, 1H), 4.45 (s, 2H), 3.79 (s, 3H), 3.72 (m, 1H), 3.65-3.58 (m, 4H), 2.96 (d, J = 2.8 Hz, 1H), 2.21 (m, 1H), 2.11 (t, J = 6.4 Hz, 2H), 1.96 (m, 1H), 1.72-1.49 (m, 8H), 1.21 (m, 1H), 0.88 (m, 12H), 0.07 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 159.6, 130.3, 129.6, 123.2, 114.1, 76.0, 73.3, 69.9, 63.3, 55.5, 39.0, 36.7, 36.3, 33.4, 32.8, 31.2, 31.0, 26.2, 25.8, 18.6, 15.3, 0.7, -4.9; **IR** (neat) cm-1 3472, 2952, 2930, 2858, 1612, 1514, 1463, 1248, 1098, 1038, 836, 775; **HRMS** (ESI) Calculated for $C_{30}H_{57}O_4Si_2$ [M+1] 537.3795, found 537.3802; $[\propto]_D^{20}$ = -4.1° (*c* = 1.7 mg/mL, $CHCl_3$).



25 **22** **26**

(2S,3*R*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2-methyl-7-((trimethylsilyl)methylene)undecan-3-ol (26): Obtained, after column chromatography, 88% (average of two runs) as a colorless oil.

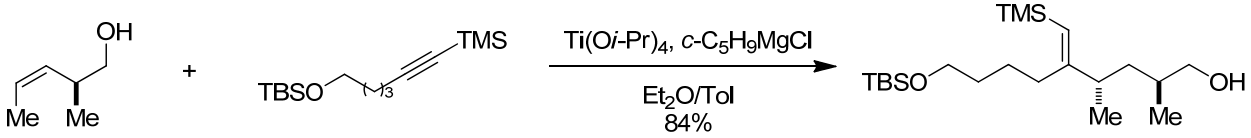
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8, 2H), 5.17 (s, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.74 (m, 1H), 3.60 (t, J = 6.4 Hz, 2H), 3.48 (m, 2H), 2.55 (d, J = 4.4 Hz, 1H), 2.12-2.05 (m, 4H), 1.88 (m, 1H), 1.62-1.34 (m, 8H), 0.88 (m, 12H), 0.07 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 159.5, 130.4, 129.5, 123.4, 114.1, 74.8, 74.4, 73.4, 63.4, 55.6, 39.0, 38.1, 36.2, 33.9, 33.4, 26.3, 25.8, 25.0, 18.6, 11.1, 0.7, -4.9; **IR** (neat) cm-1 3466, 2951, 2931, 2857, 1613, 1514, 1471, 1463, 1302, 1247, 1099, 1038, 836, 775; **HRMS** (ESI) Calculated for $C_{30}H_{57}O_4Si_2$ [M+1] 537.3795, found 537.3785; $[\propto]_D^{20}$ = -7.8° (*c* = 1.65 mg/mL, $CHCl_3$).



27 22 28

(2*S*,3*R*,4*R*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,4-dimethyl-7-((trimethylsilyl)methylene)undecan-3-ol (28): Obtained, after column chromatography, 74 % (average of two runs) as a light yellow oil.

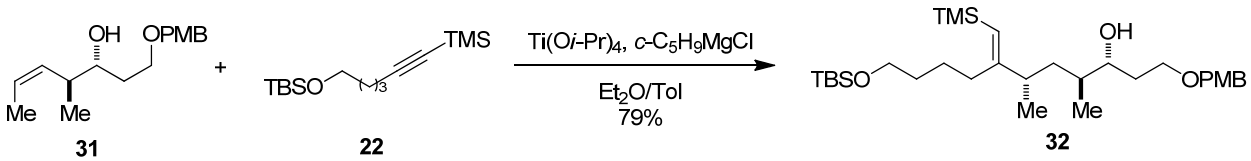
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8, 2H), 5.19 (s, 1H), 4.43 (m, 2H), 3.80 (s, 3H), 3.60 (t, J = 6 Hz, 2H), 3.52 (d, J = 4.8 Hz, 2H), 3.46 (d, J = 8.8 Hz, 1H), 2.58 (br s, 1H), 2.23-2.10 (m, 3H), 2.00-1.83 (m, 3H), 1.53-1.41 (m, 5H), 1.2 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.81 (d, J = 6.4 Hz, 3H), 0.07 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 159.5, 130.5, 129.5, 123.1, 114.1, 78.2, 75.7, 73.4, 63.4, 55.5, 36.4, 36.3, 36.3, 35.2, 33.4, 31.6, 26.3, 25.8, 18.6, 15.9, 9.9, 0.7, -4.9; **IR** (neat) cm^{-1} 3501, 2953, 2930, 2857, 1612, 1514, 1462, 1302, 1247, 1099, 836, 775; **HRMS** (ESI) Calculated for $C_{31}H_{59}O_4Si_2$ [M+1] 551.3952, found 551.3945; $[\propto]_D^{20}$ = -15.6° (*c* = 1.85 mg/mL, $CHCl_3$).



29 22 30

(2*S*,4*S*,*E*)-9-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl-5-((trimethylsilyl)methylene)nonan-1-ol (30): Obtained, after column chromatography, 84 % (average of two runs) as a colorless oil.

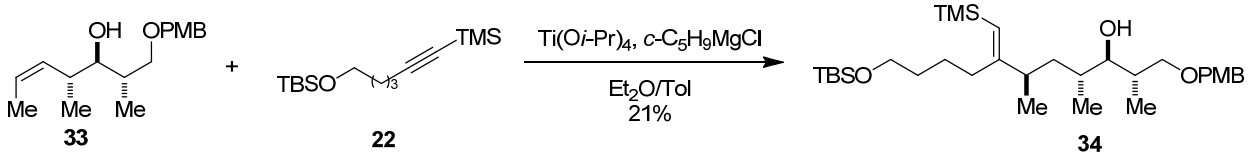
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 1H), 3.60 (t, J = 6.4 Hz, 2H), 3.46 (m, 1H), 3.41 (m, 1H), 2.16-2.07 (m, 3H), 1.64 (m, 1H), 1.42-1.27 (m, 4H), 1.24-1.16 (m, 2H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (m, 12H), 0.08 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8, 120.7, 69.0, 63.3, 40.6, 38.1, 36.5, 33.9, 33.6, 26.7, 26.3, 20.8, 18.6, 16.9, 0.8, -4.9; **IR** (neat) cm-1 3339, 2929, 2954, 2858, 1610, 1471, 1462, 1247, 1101, 835, 774; **HRMS** (ESI) Calculated for $C_{21}H_{47}O_2Si_2$ [M+1] 387.3115, found 387.3109; $[\propto]_D^{20}$ = 7.3° (*c* = 2.85 mg/mL, $CHCl_3$).



31 22 32

(3*R*,4*S*,6*S*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4,6-dimethyl-7-((trimethylsilyl)methylene)undecan-3-ol (32): Obtained, after column chromatography, 79 % (average of two runs) as a light yellow oil.

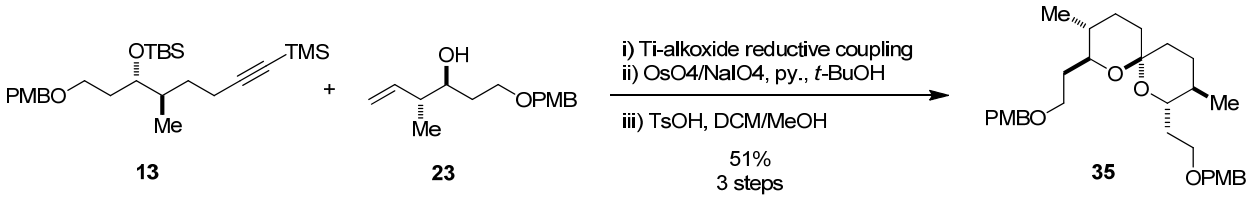
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.18 (s, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.72 (dt, *J* = 9.7, 5.0 Hz, 1H), 3.62 (dt, *J* = 9.4, 5.4 Hz, 4H), 2.93 (d, *J* = 2.6 Hz, 1H), 2.12 (dt, *J* = 15.6, 5.4 Hz, 3H), 1.82 – 1.11 (m, 10H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 – 0.77 (m, 12H), 0.08 (s, 8H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 159.6, 130.3, 129.6, 120.4, 114.1, 76.5, 73.4, 69.9, 63.4, 55.6, 39.8, 37.9, 36.9, 36.6, 33.6, 32.9, 26.6, 26.3, 20.1, 18.6, 15.3, 0.8, -4.9; **IR** (neat) cm^{-1} 3484, 2953, 2929, 2857, 1611, 1513, 1462, 1302, 1247, 1097, 1038, 836, 775; **HRMS** (ESI) Calculated for $C_{31}H_{59}O_4Si_2$ [M+1] 551.3952, found 551.3945; $[\propto]_D^{20}$ = -14.1° (*c* = 1.55 mg/mL, $CHCl_3$).



33 22 34

(2*S*,3*R*,4*R*,6*R*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,4,6-trimethyl-7-((trimethylsilyl)methylene)undecan-3-ol (34): Obtained, after column chromatography, 21 % (average of two runs) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.24 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4, 2H), 5.17 (s, 1H), 4.43 (m, 2H), 3.79 (s, 3H), 3.60 (m, 3H), 3.44 (m, 1H), 3.37 (m, 1H), 3.30 (m, 1H), 2.11 (m, 3H), 1.98 (m, 1H), 1.61-1.25 (m, 7H), 0.95 (d, J = 6.4 Hz, 3H), 0.88 (m, 12H), 0.07 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 166.6, 159.6, 130.1, 129.7, 120.1, 114.1, 81.8, 75.7, 73.5, 63.4, 55.5, 37.5, 37.1, 36.6, 35.7, 33.7, 33.6, 26.5, 26.3, 19.6, 18.6, 17.3, 14.4, 0.8, -4.9; **IR** (neat) cm-1 1 3507, 2955, 2929, 2857, 1612, 1514, 1462, 1247, 1173, 1097, 1038, 836, 775; **HRMS** (ESI) Calculated for $C_{32}H_{61}O_4Si_2$ [M+1] 565.4108, found 565.4104; $[\propto]_D^{20}$ = +5.3° (*c* = 2.05 mg/mL, $CHCl_3$).

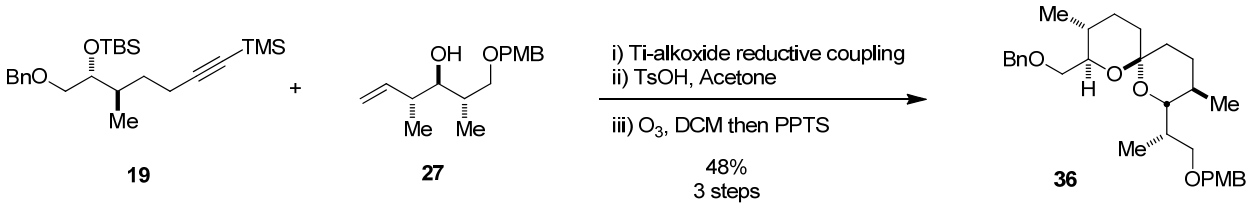


13 23 35

(2*S*,3*R*,6*R*,8*S*,9*R*)-2,8-bis(2-((4-methoxybenzyl)oxy)ethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (35):

Olefin **23** (0.020 g, 0.080 mmol) was reductively coupled to alkyne **13** (0.092 g, 0.20 mmol) following the general procedure described. After passage through a short silica plug (8:1 → 4:1 hexanes:EtOAc), the coupled product was dissolved in *t*-BuOH (0.5 mL), pyridine was added (0.010 mL, 0.12 mmol), followed by OsO_4 (0.153 mL, 4% aq, 0.0024 mmol) then finally $NaIO_4$ (0.24 mL, 0.5M aq, 0.12 mmol) all at room temperature. The reaction mixture was allowed to stir for 16 hours, quenched with brine (2 mL), extracted with EtOAc (3 x 5 mL), and the organic layer was dried over $MgSO_4$ and concentrated. The crude material was dissolved in 1 mL DCM/MeOH (2:1), and a small spatula tip of TsOH was added at room temperature and the solution was stirred for 12 hours. The reaction mixture was then diluted with EtOAc (5 mL), washed with (sat) $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated. Column chromatography (10% EtOAc/Hexanes) provided spiroketal **35** as a colorless oil (0.011 g, 52% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.36 (q, *J* = 11.3 Hz, 2H), 3.77 (s, 3H), 3.61 (td, *J* = 8.5, 4.6 Hz, 1H), 3.53 (dd, *J* = 16.4, 7.5 Hz, 1H), 3.27 (td, *J* = 10.2, 2.3 Hz, 1H), 1.98 (dtd, *J* = 10.2, 7.8, 2.4 Hz, 1H), 1.63 – 1.52 (m, 5H), 1.52 – 1.39 (m, 3H), 1.36 – 1.21 (m, 2H), 0.82 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 131.1, 129.6, 114.0, 95.3, 73.1, 72.0, 67.6, 55.6, 36.2, 35.5, 33.7, 28.6, 18.3; **IR** (neat) cm-1 2950, 2925, 2858, 1613, 1513, 1456, 1301, 1248, 1173, 1100, 1063, 1037, 994; **HRMS** (ESI) Calculated for $C_{31}H_{45}O_6$ [M+1] 513.3216, found 513.3208; $[\propto]_D^{20}$ = -24.8 (*c* = 2.50 mg/mL, $CHCl_3$).

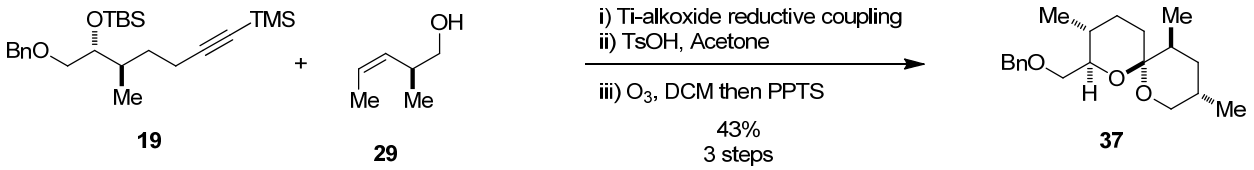


19 27 36

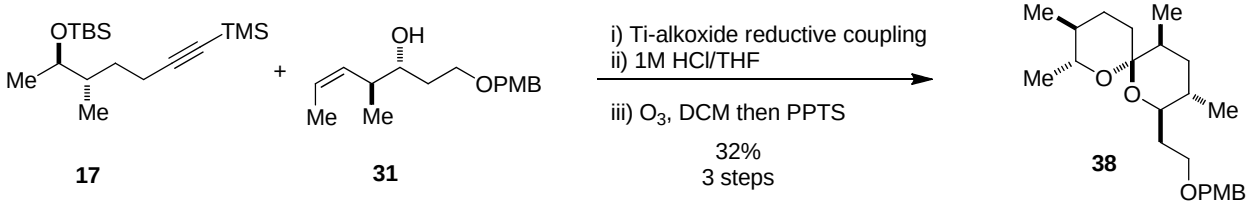
(2*R*,3*R*,6*S*,8*R*,9*R*)-2-((benzyloxy)methyl)-8-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (36):[22]

Olefin **27** (0.040 g, 0.150 mmol) was reductively coupled to alkyne **19** (0.159 g, 0.375 mmol) following the general procedure described. After passage through a short silica plug (5% → 10% EtOAc/hexanes), 35mg of the coupled product was dissolved in acetone (5 mL) at room temperature, 56mg of TsOH was added, and the resulting solution was stirred for 12 hours. The reaction mixture was then diluted with EtOAc (15 mL), washed with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated. The resulting oil was dissolved in 5 mL DCM and a drop of a Sudan III solution (in DCM) was added to achieve a slight pink color. The mixture was cooled to -78 °C and ozone was bubbled

through until the pink color just disappeared, then the ozonide was reduced by the addition of 1 mL dimethyl sulfide. After allowing the reaction mixture to warm to room temperature and stir for 20 minutes, a spatula tip of TsOH was added, and the solution was stirred for an additional 5 hours. The resulting solution was then diluted with DCM (10 mL), washed with sat. $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated. Preparative TLC (eluting 2 x with 3 % EtOAc/hexanes and 1 x with 9 % EtOAc/hexanes) yielded spiroketal **36** as a colorless oil (0.012 g, 48 % over three steps).
^{1}H NMR (400 MHz, C6D6); δ 7.31 (dd, *J* = 18.0, 8.0 Hz, 4H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.86 – 6.72 (m, 2H), 4.60 – 4.30 (m, 4H), 3.99 (dt, *J* = 10.3, 3.3 Hz, 1H), 3.68 – 3.51 (m, 3H), 3.36 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.32 – 3.19 (m, 4H), 2.18 – 2.02 (m, 2H), 1.79 (ddd, *J* = 17.9, 11.0, 4.1 Hz, 2H), 1.62 (dt, *J* = 7.0, 3.7 Hz, 1H), 1.56 – 1.18 (m, 7H), 1.11 (ddd, *J* = 26.3, 17.7, 10.2 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.59 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 159.4, 139.1, 131.1, 129.6, 128.5, 128.2, 127.7, 114.0, 97.6, 77.5, 76.1, 73.8, 73.6, 73.1, 71.6, 55.6, 36.6, 35.0, 31.7, 31.5, 30.2, 28.5, 27.5, 18.1, 17.2, 10.1; **IR** (neat) cm-1 2925, 2856, 1613, 1513, 1457, 1378, 1357, 1248, 1172, 1112, 1093, 1024, 815, 697; **HRMS** (ESI) Calculated for $C_{30}H_{43}O_5$ [M+1] 483.3110, found 483.3096; $[\propto]_D^{20}$ = -10.0 (*c* = 2mg/mL, $CHCl_3$).



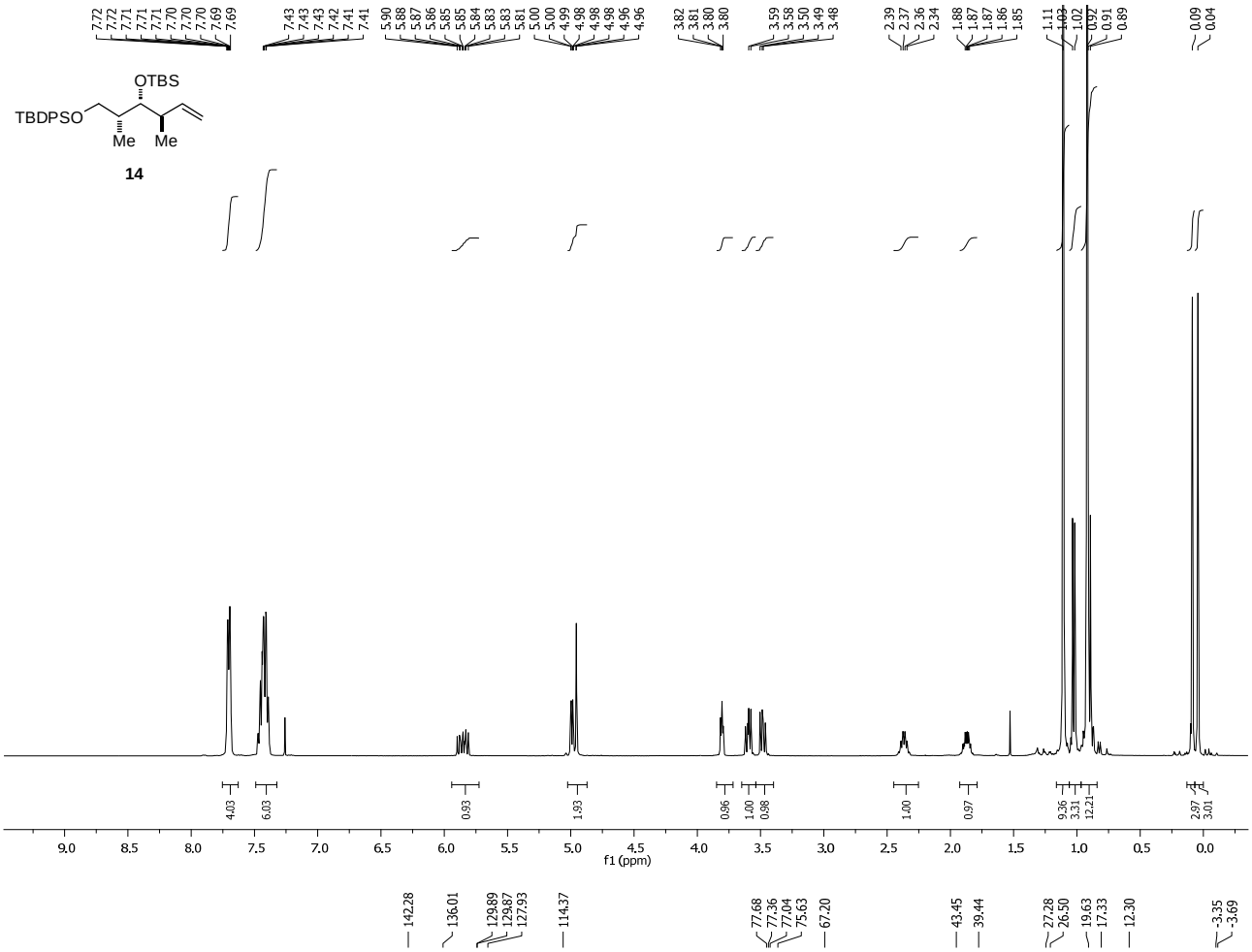
(2*R*,3*R*,6*S*,9*S*,11*S*)-2-((benzyloxy)methyl)-3,9,11-trimethyl-1,7-dioxaspiro[5.5]undecane (37):
Olefin **29** (0.019 g, 0.19 mmol) was reductively coupled to alkyne **19** (0.20 g, 0.475 mmol) following the general procedure described. After passage through a short silica plug (10% EtOAc/hexanes), 20mg of the coupled product was dissolved in acetone (2 mL) at room temperature, 32mg of TsOH was added, and the resulting solution was stirred for 12 hours. The reaction mixture was then diluted with EtOAc (10 mL), washed with sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated. The resulting oil was dissolved in 5 mL DCM and a drop of a Sudan III solution (in DCM) was added to achieve a slight pink color. The mixture was cooled to -78 °C and ozone was bubbled through until the pink color just disappeared, then the ozonide was reduced by the addition of 1 mL dimethyl sulfide. After allowing the reaction mixture to warm to room temperature and stir for 20 minutes, a spatula tip of TsOH was added, and the resulting solution was stirred for an additional 5 hours. Finally, the resulting solution was diluted with DCM (10 mL), washed with sat. $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated. Preparative TLC (eluting 3 x with 3 % EtOAc/hexanes) yielded spiroketal **37** as a colorless oil (0.009 g, 43 % over three steps).
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.41 – 7.27 (m, 4H), 4.65 (q, *J* = 12.4 Hz, 2H), 3.83 (dd, *J* = 11.0, 2.9 Hz, 1H), 3.62 (ddd, *J* = 16.5, 11.2, 3.9 Hz, 2H), 3.43 (ddd, *J* = 9.6, 5.3, 2.4 Hz, 1H), 3.27 (dd, *J* = 11.0, 1.4 Hz, 1H), 1.80 (dtd, *J* = 16.0, 12.3, 5.9 Hz, 4H), 1.67 – 1.49 (m, 4H), 1.45 (ddd, *J* = 12.8, 3.7, 2.3 Hz, 1H), 1.38 – 1.21 (m, 4H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$); δ 139.43, 128.62, 127.74, 127.66, 98.20, 75.71, 73.73, 71.88, 64.89, 33.98, 33.15, 31.95, 31.48, 28.82, 28.18, 18.07, 17.51, 17.09; **IR** (neat) cm-1 2956, 2927, 2872, 1660, 1455, 1376, 1260, 1223, 1088, 993, 800, 733, 696; **HRMS** (ESI) Calculated for $C_{20}H_{31}O_3$ [M+1] 319.2273, found 319.2273; $[\propto]_D^{20}$ = -21.0 (*c* = 5.0 mg/mL, $CHCl_3$).



(2*R*,3*S*,5*S*,6*S*,8*R*,9*S*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3,5,8,9-tetramethyl-1,7-dioxaspiro[5.5]undecane (38):
Olefin **31** (0.037 g, 0.140 mmol) was reductively coupled to alkyne **17** (0.108 g, 0.35 mmol) following the general procedure described. After passage through a short silica plug (10% EtOAc/hexanes), 25mg of the coupled product was dissolved in 0.6 mL 1M HCl/THF (1/1) at room temperature, a few drops of EtOH were added and the reaction mixture was stirred at room temperature for 18 hours. The resulting solution was then diluted with EtOAc (5 mL), washed with sat. $NaHCO_3$ (2 mL), brine (2 mL), dried over $MgSO_4$ and concentrated. The resulting oil was dissolved in 1 mL DCM and a

drop of a Sudan III solution (in DCM) was added to achieve a slight pink color. The mixture was cooled to -78 °C and ozone was bubbled through until the pink color just disappeared, then the ozonide was reduced by the addition of 0.2 mL dimethyl sulfide. After allowing the reaction mixture to warm to room temperature and stir for 20 minutes, a spatula tip of TsOH was added and the solution was stirred for an additional 5 hours. The reaction mixture was then diluted with DCM (5 mL), washed with sat. $NaHCO_3$ (2 mL), dried over $MgSO_4$ and concentrated. Column chromatography (eluting with 5 % EtOAc/hexanes) yielded spiroketal **38** as a colorless oil (0.009 g, 32 % over three steps).

^{1}H NMR (400 MHz, C6D6); δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.39 (q, *J* = 11.5 Hz, 2H), 3.81 (td, *J* = 9.0, 5.2 Hz, 1H), 3.66 – 3.61 (m, 1H), 3.61 – 3.53 (m, 1H), 3.49 (dq, *J* = 9.8, 6.2 Hz, 1H), 3.29 (s, 3H), 2.19 – 2.02 (m, 2H), 1.83 – 1.72 (m, 2H), 1.66 – 1.56 (m, 2H), 1.46 (dddd, *J* = 13.0, 11.1, 6.6, 3.3 Hz, 2H), 1.39 – 1.31 (m, 1H), 1.28 (dd, *J* = 13.1, 4.6 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 5H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 159.4, 131.1, 129.5, 114.0, 97.9, 73.0, 71.7, 71.4, 67.3, 55.6, 36.9, 36.5, 35.8, 33.8, 33.5, 29.6, 28.4, 19.9, 18.2, 18.5, 15.5; **IR** (neat) cm-1 2962, 2926, 2857, 1729, 1614, 1586, 1513, 1458, 1378, 1301, 1247, 1172, 1106, 1070, 1029, 986, 820; **HRMS** (ESI) Calculated for $C_{23}H_{37}O_4$ [M+1] 377.2692, found 377.2686; $[\propto]_D^{20}$ = +23.3° (*c* = 3.0 mg/mL, $CHCl_3$).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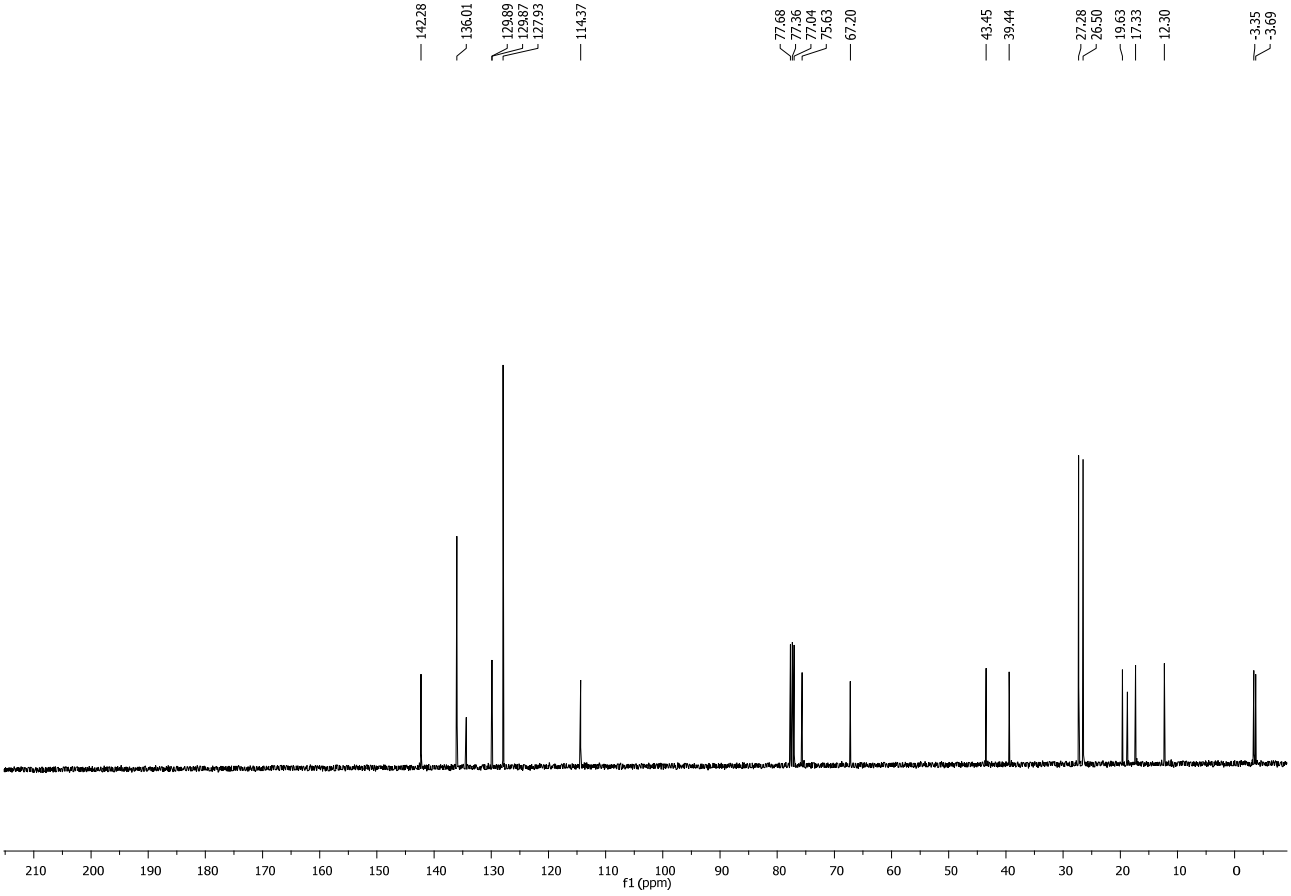
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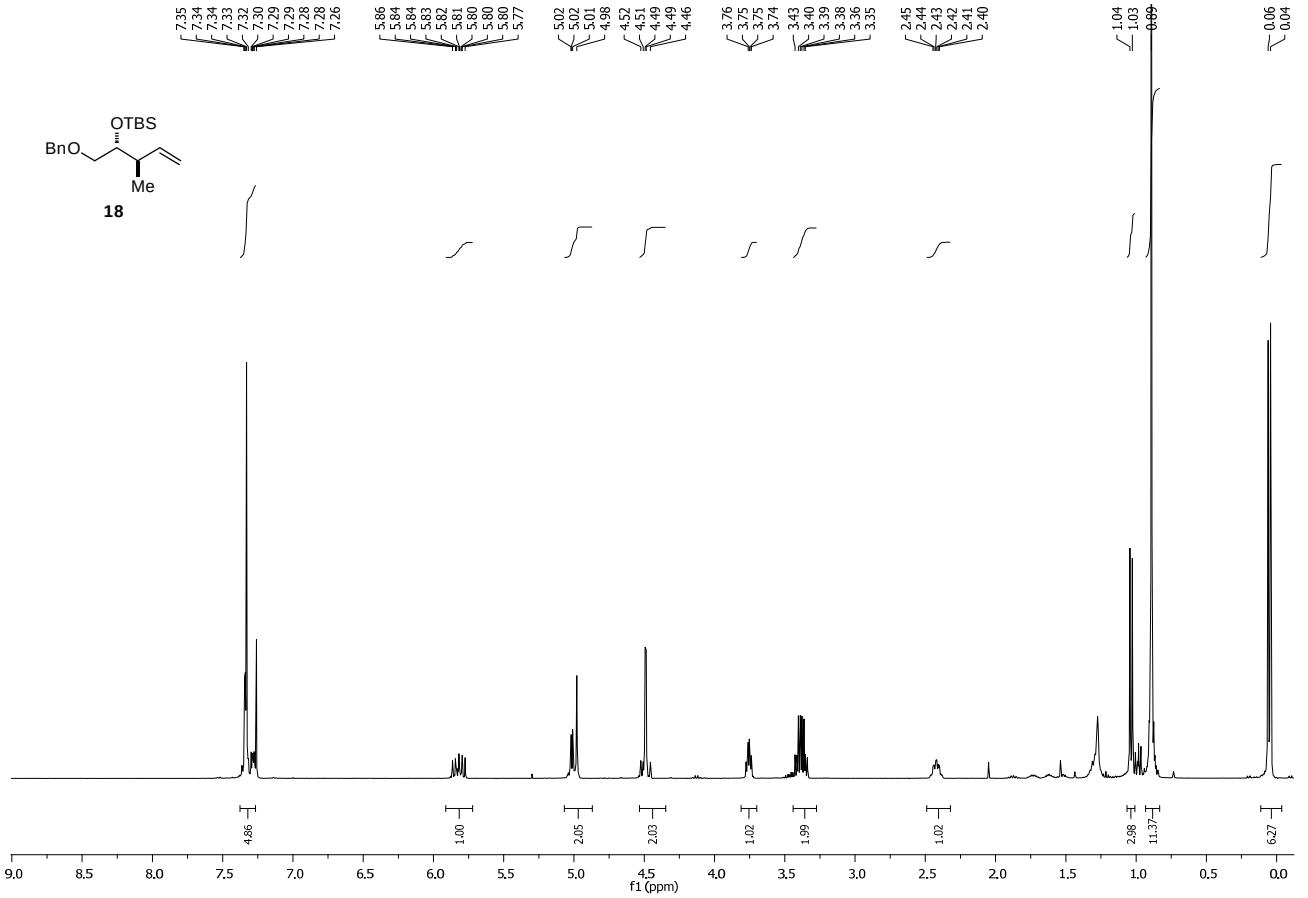
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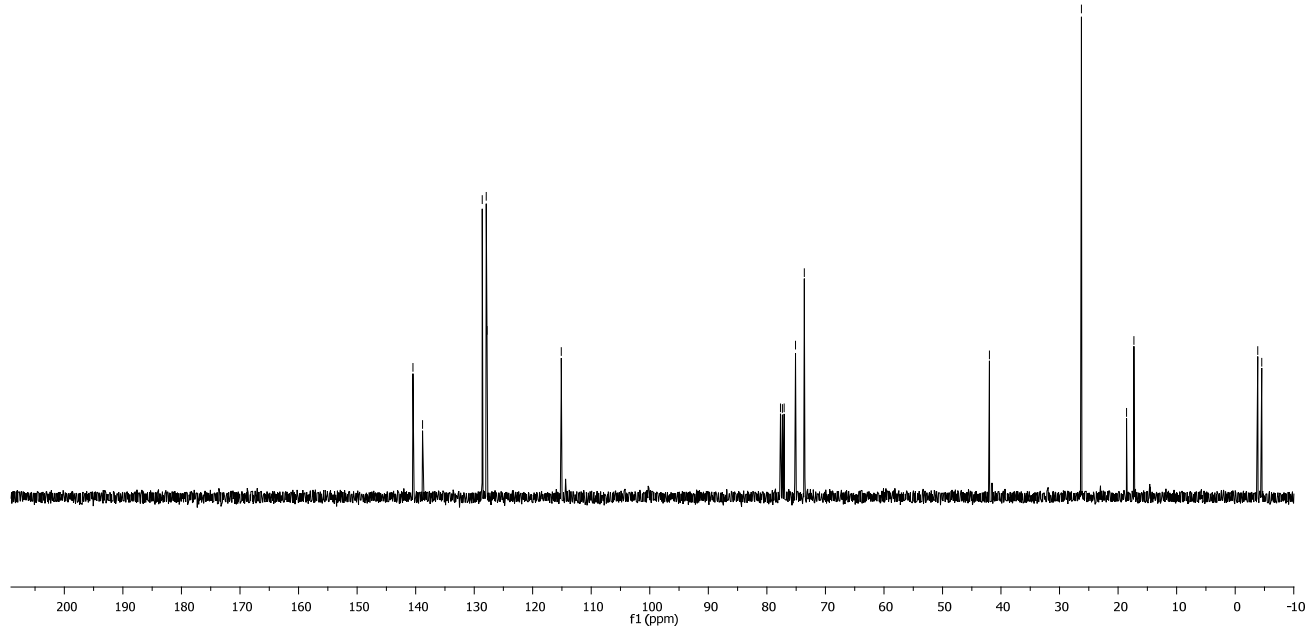
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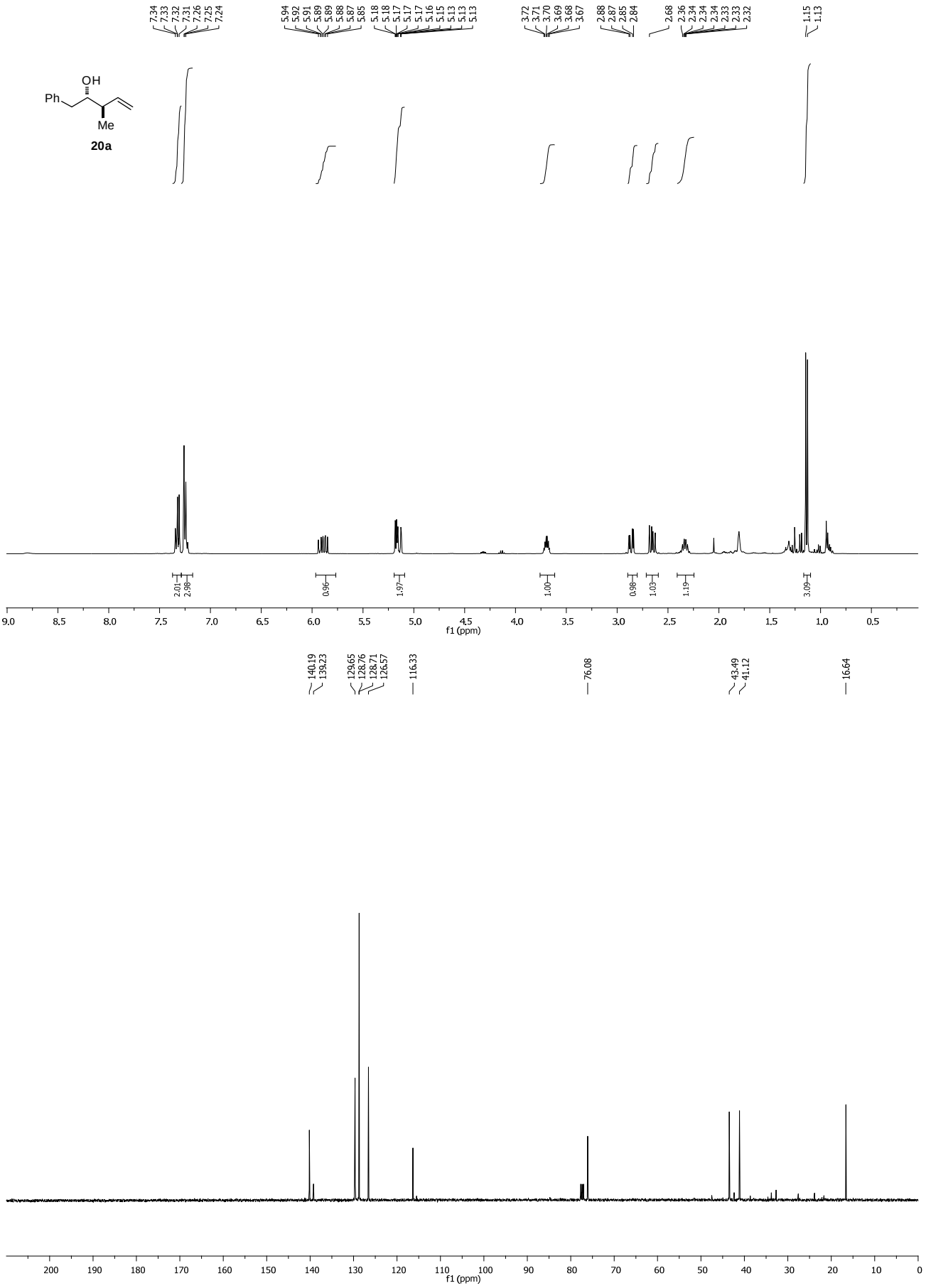
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1.13
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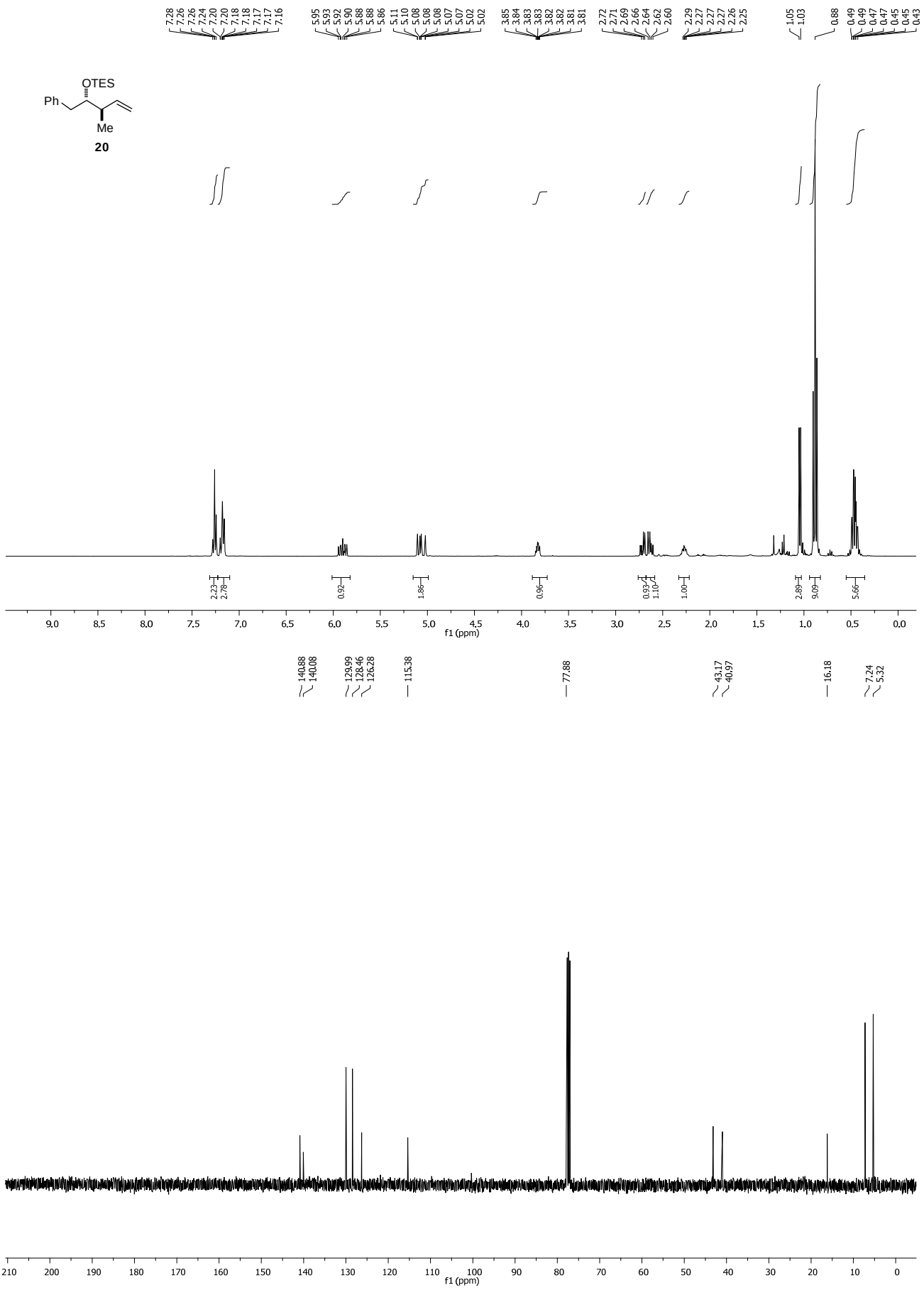
f1 (ppm)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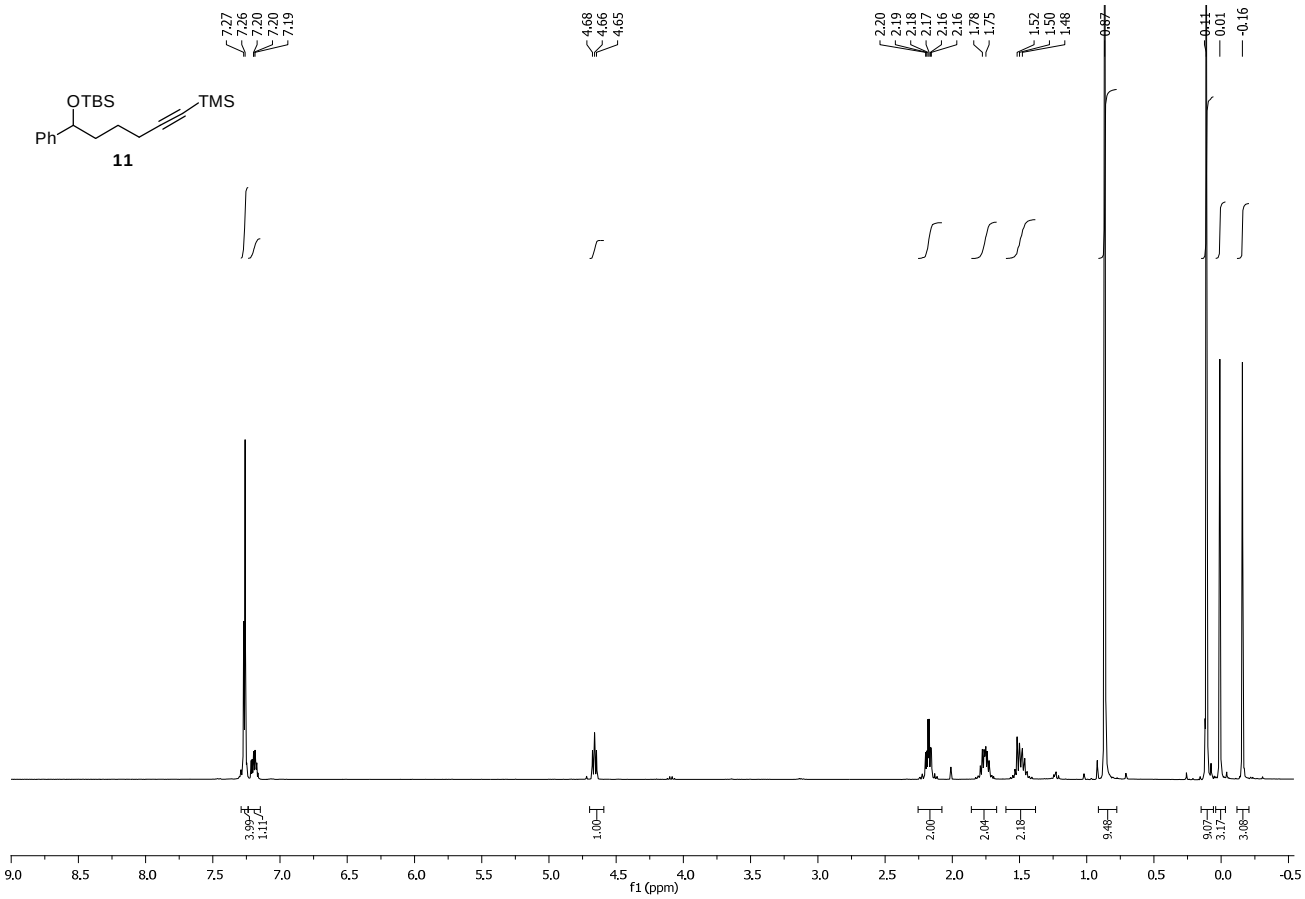
f1 (ppm)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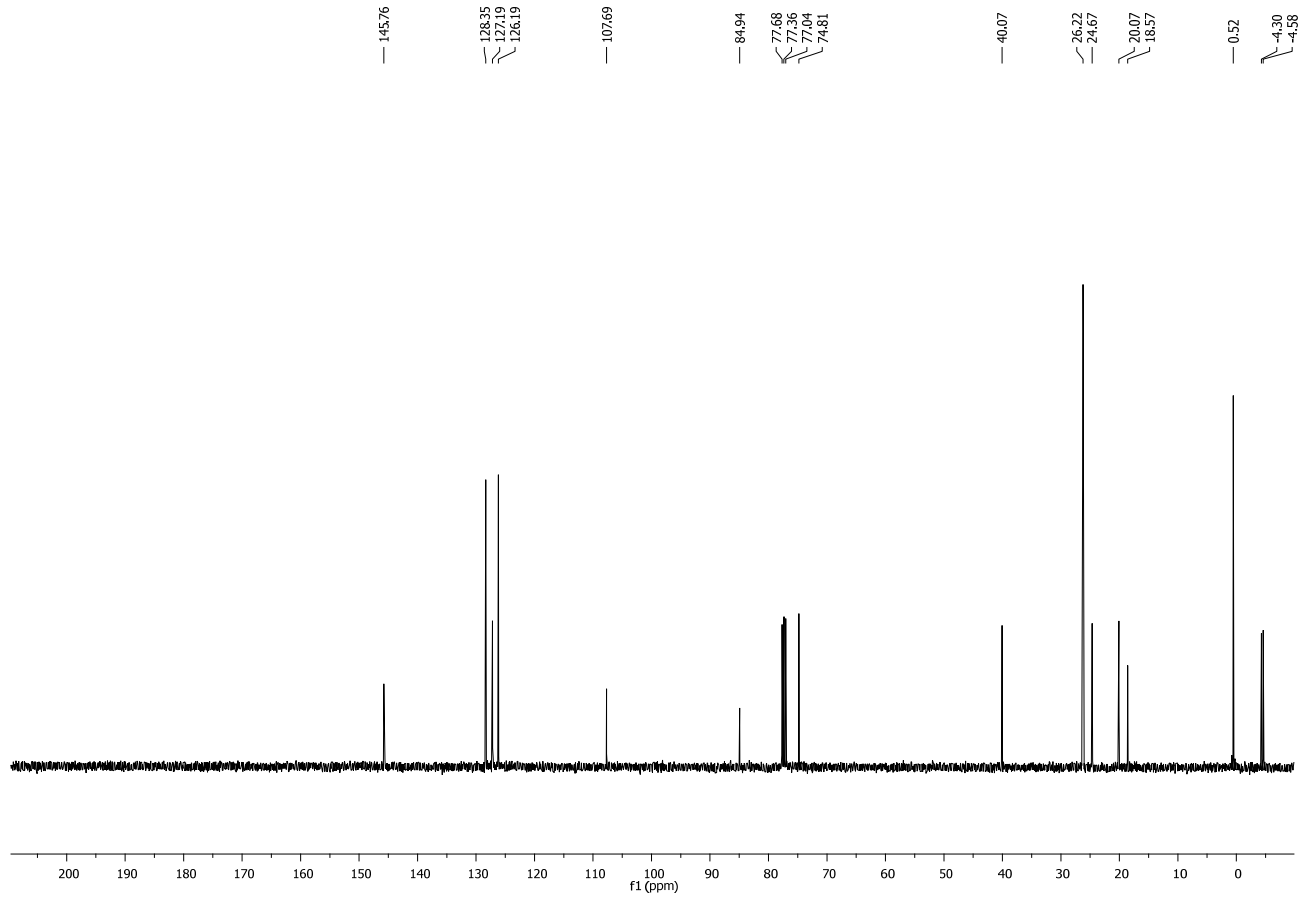
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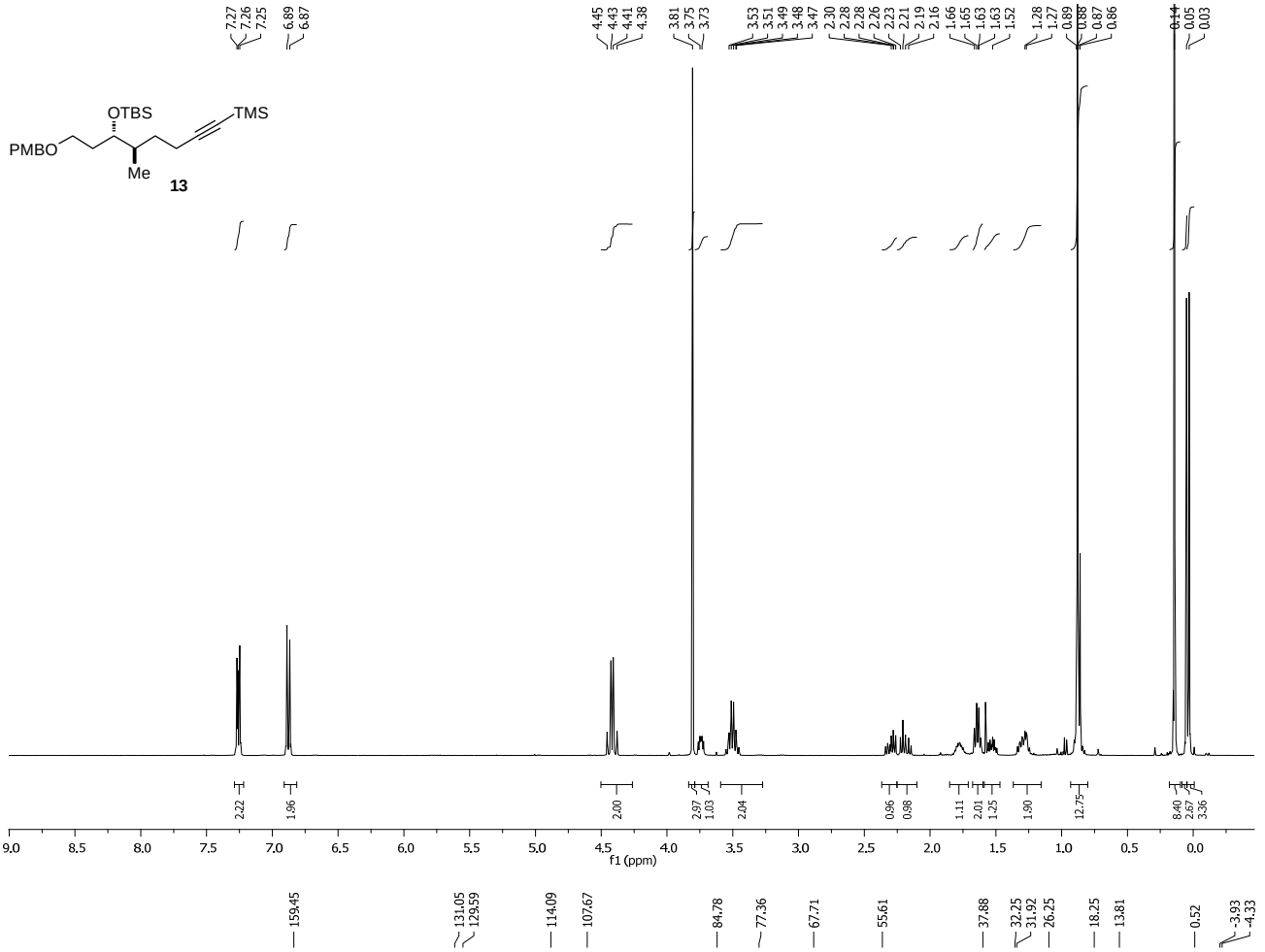
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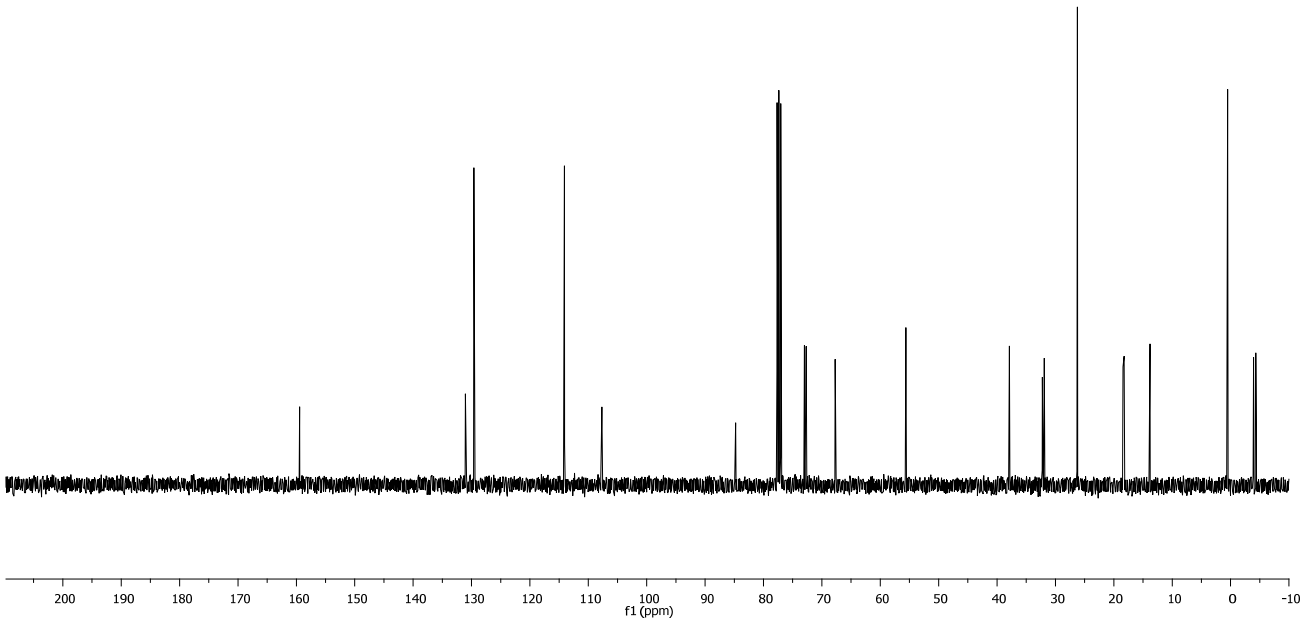
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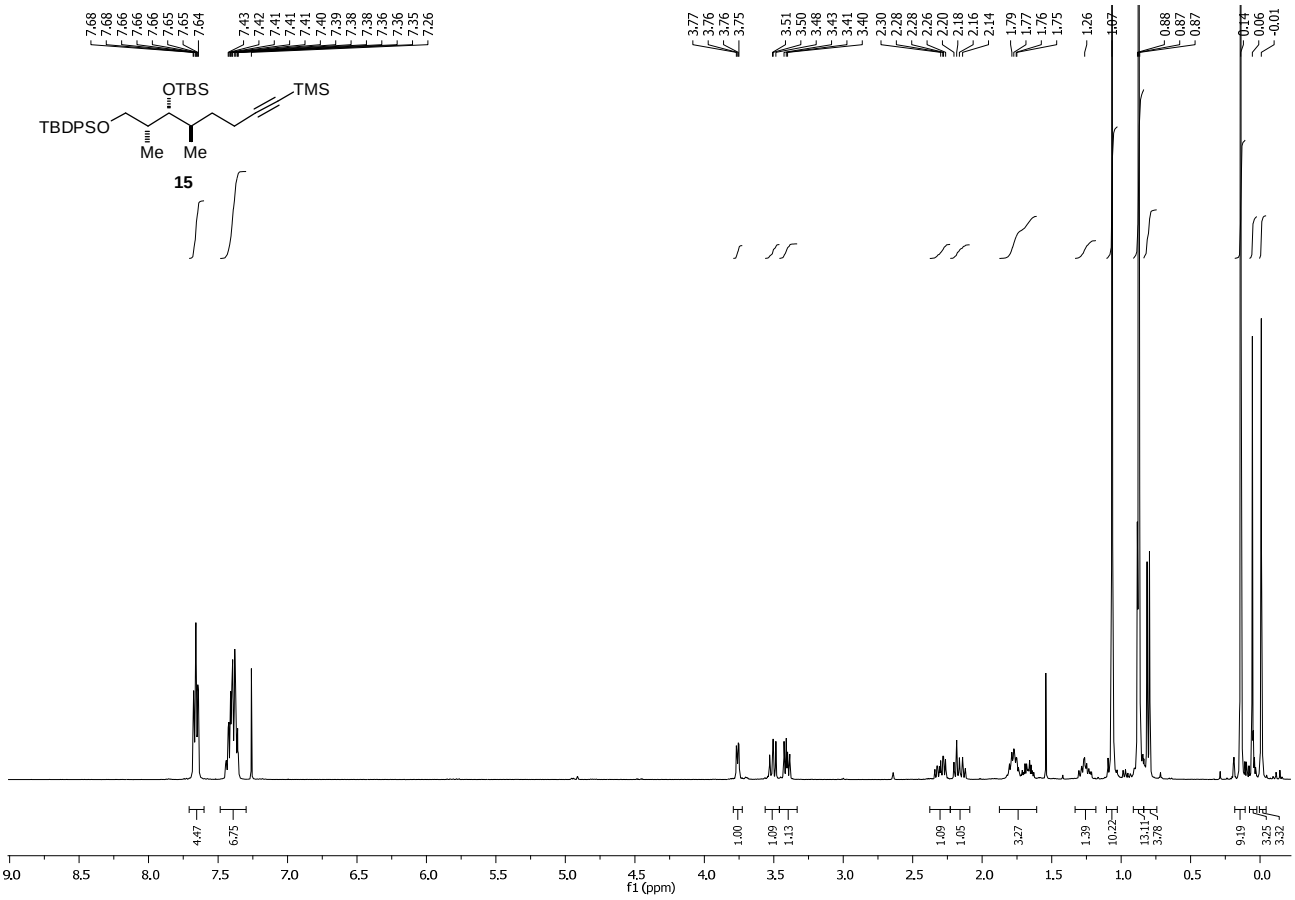
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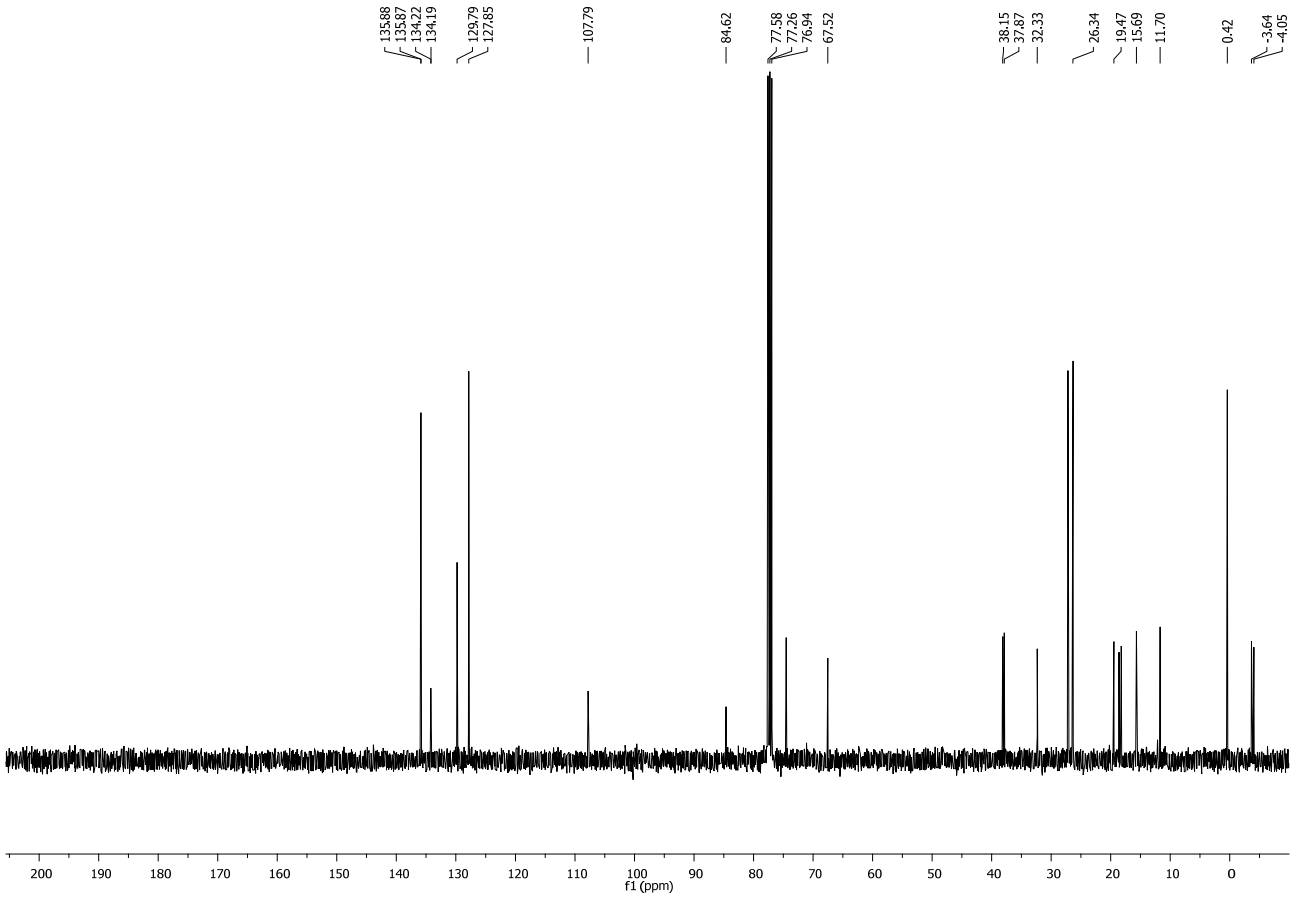
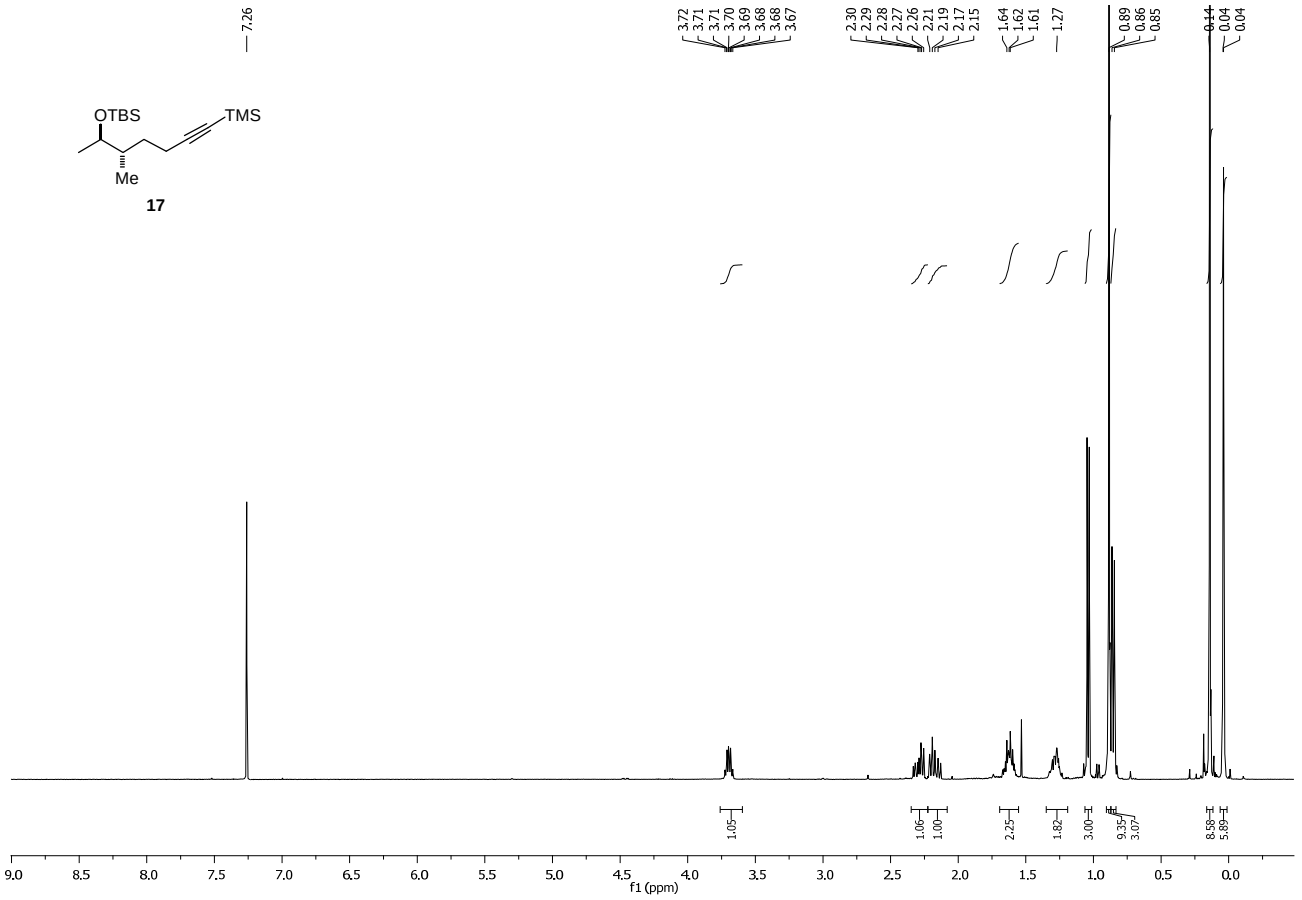

f1 (ppm)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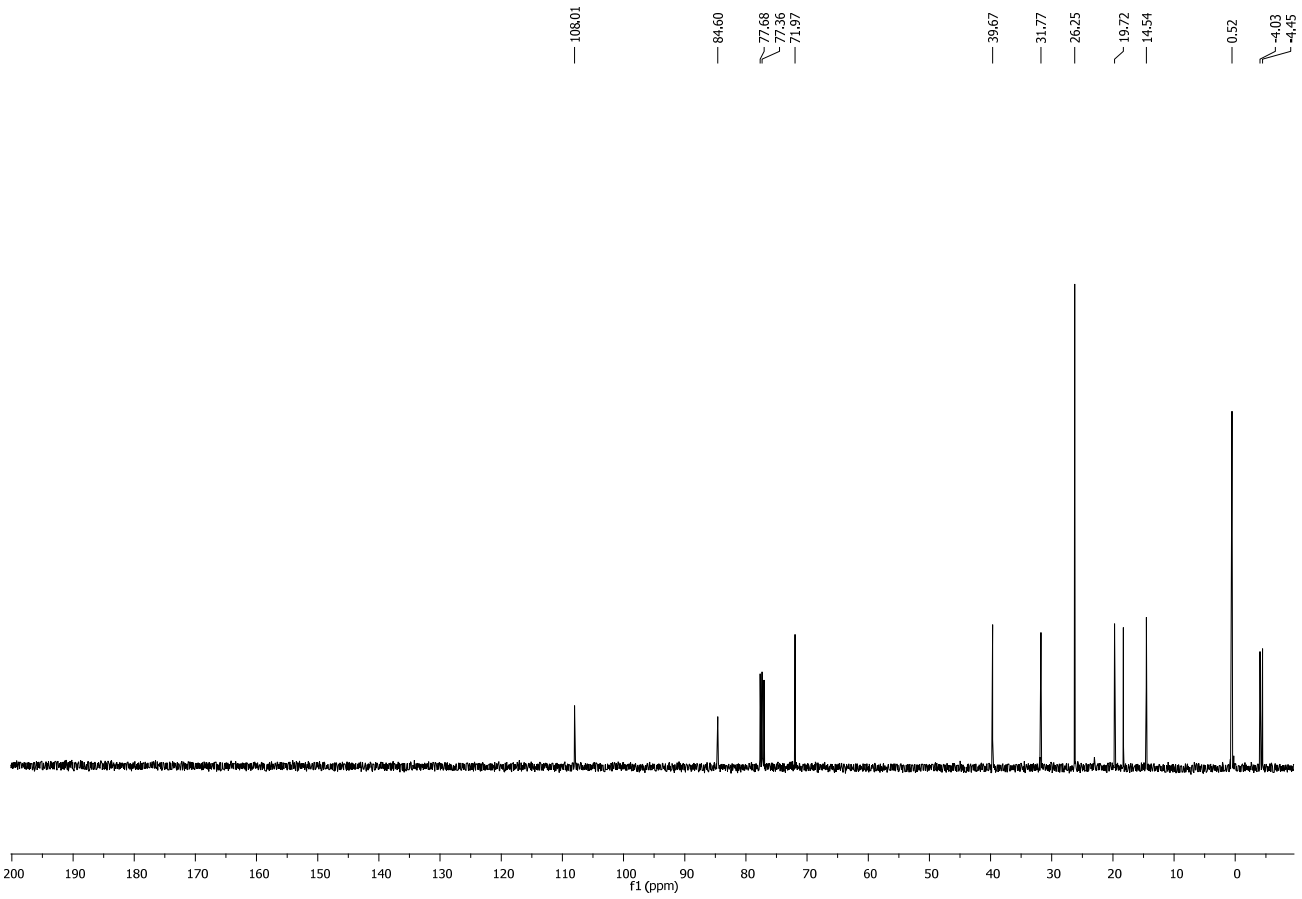
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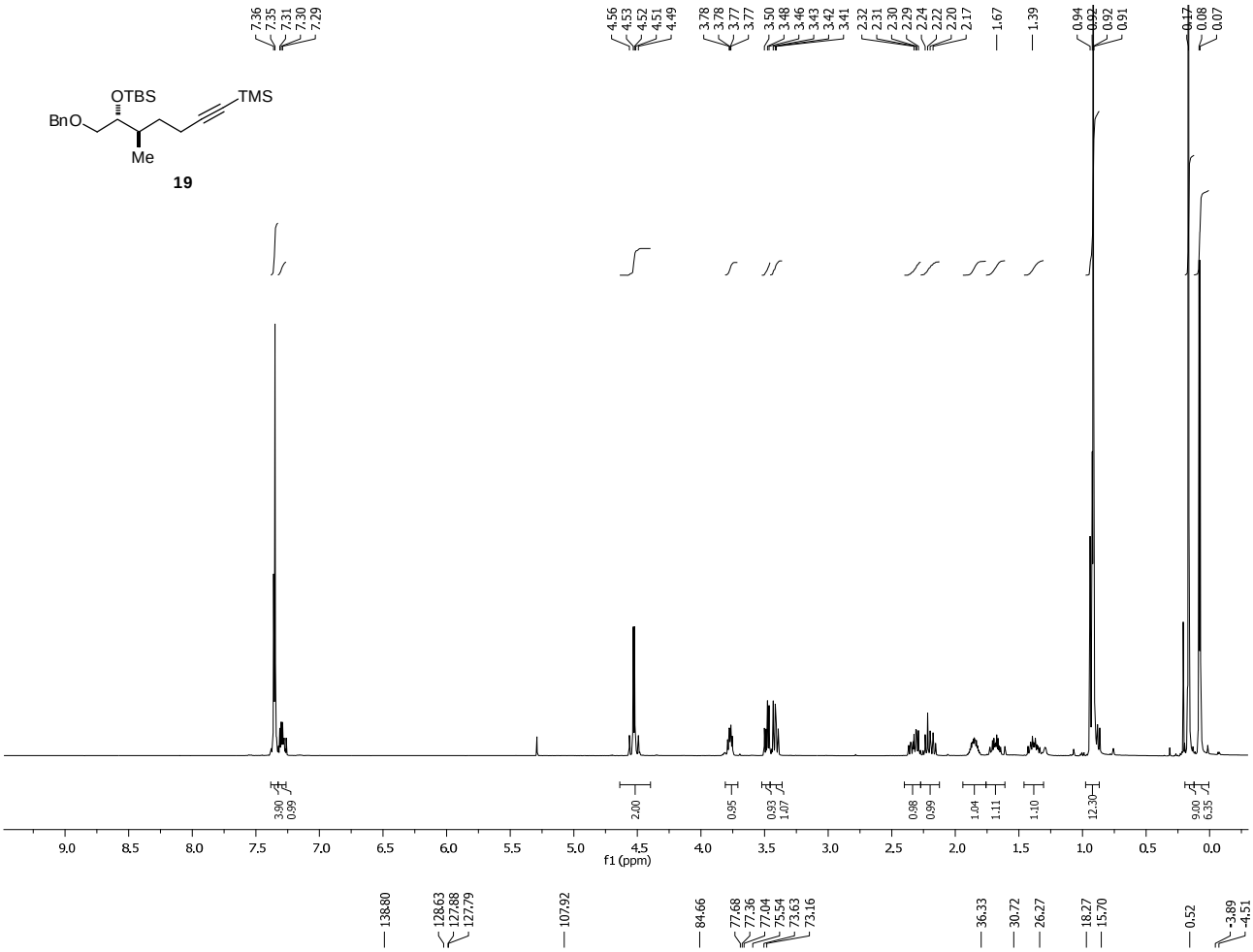
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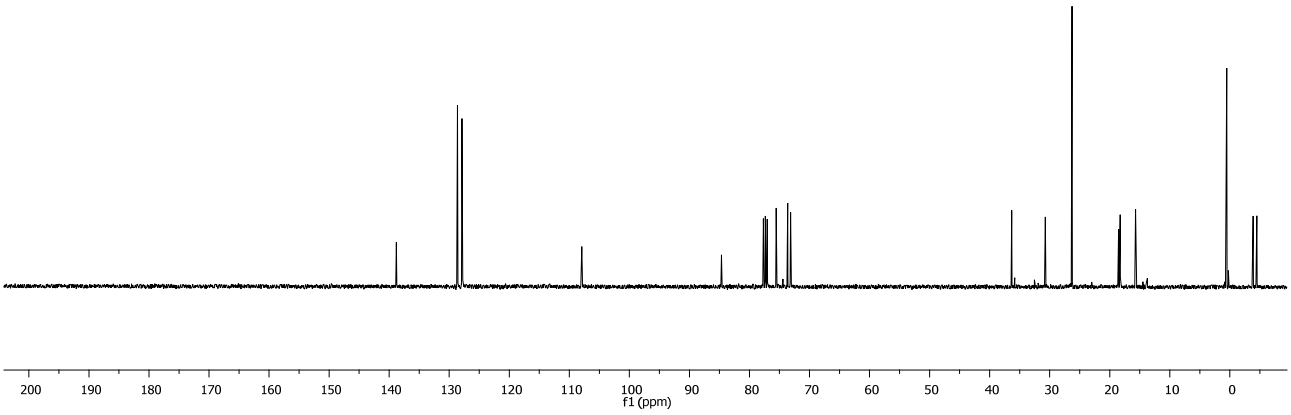
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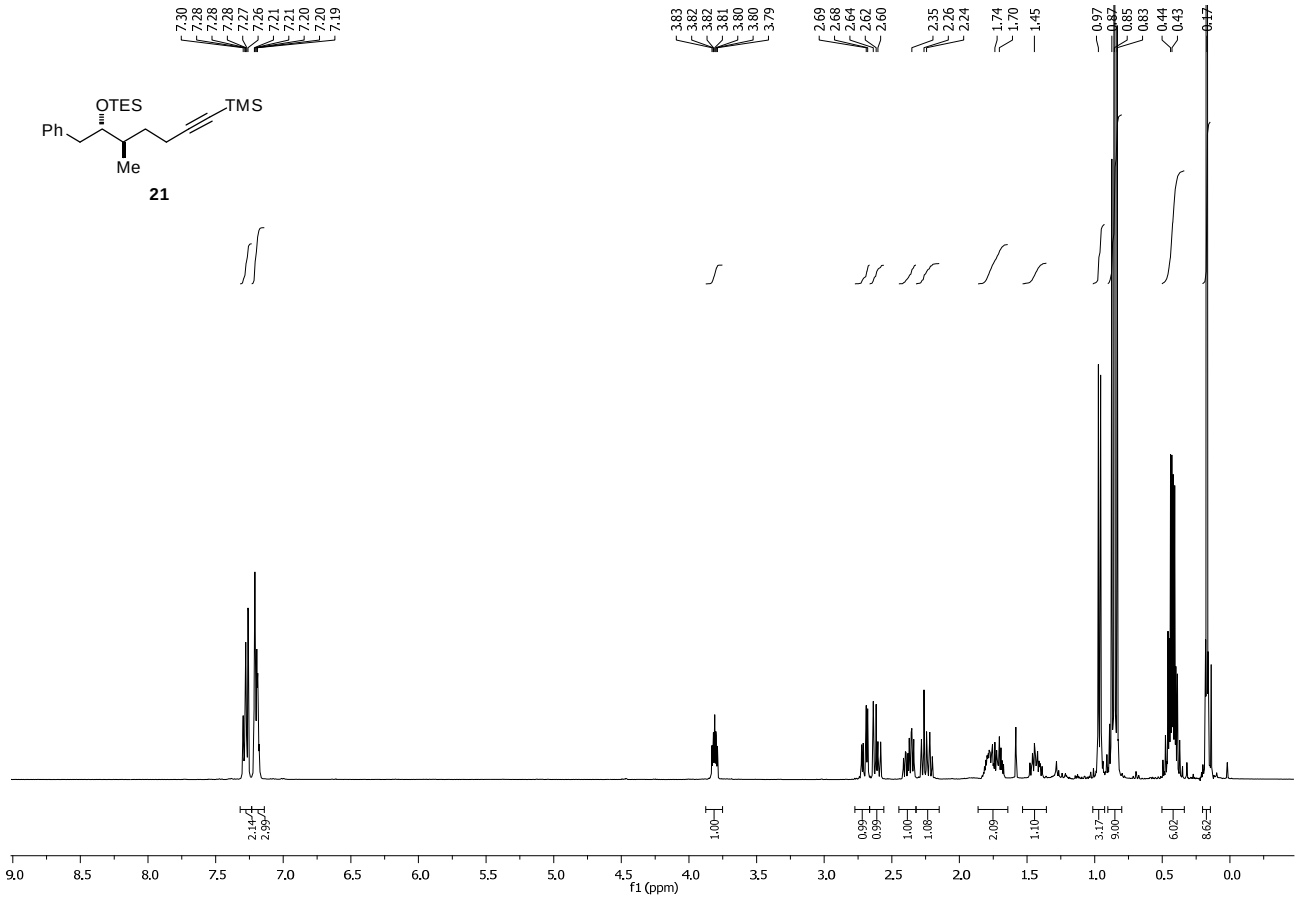
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1.45
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OTES
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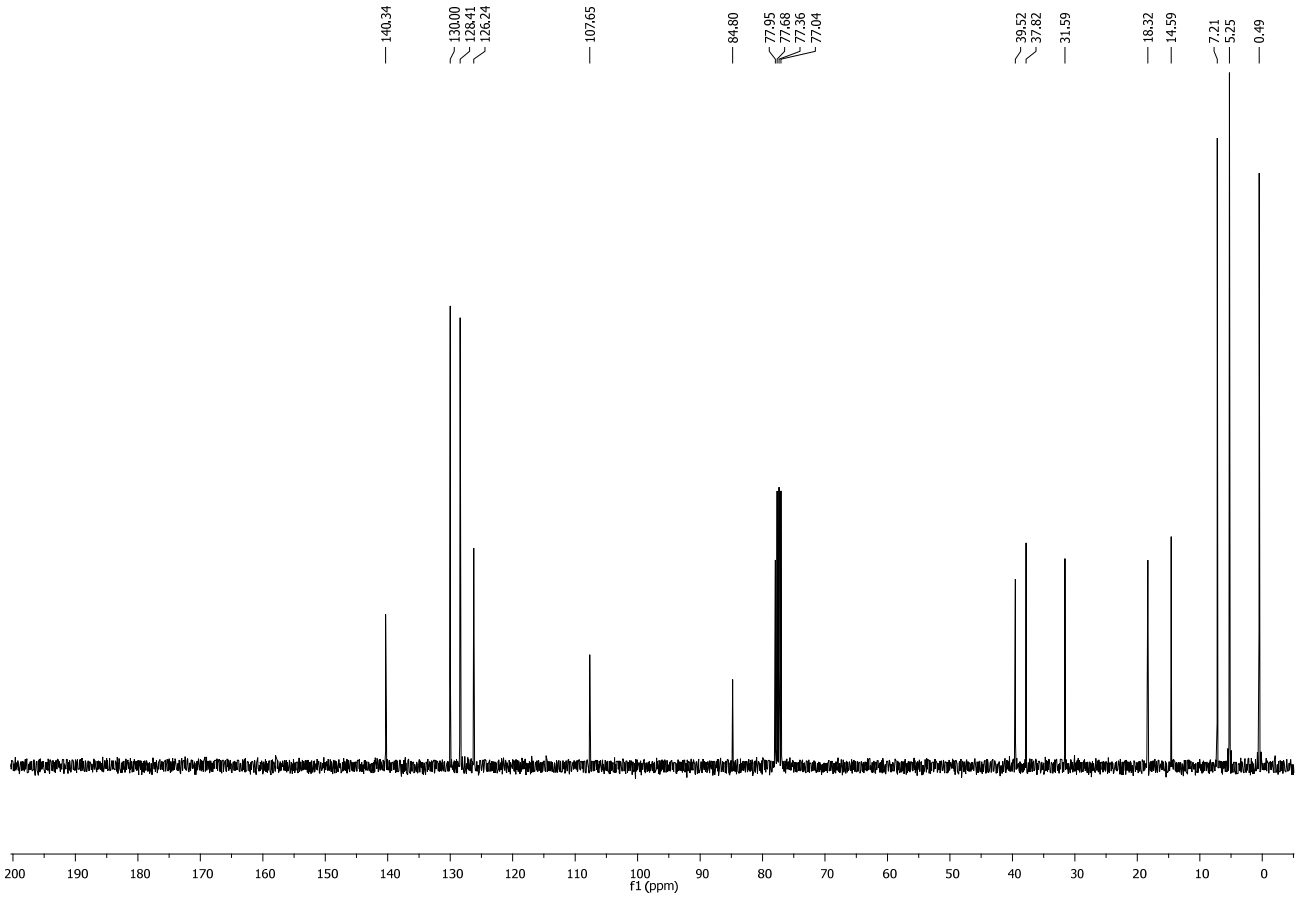
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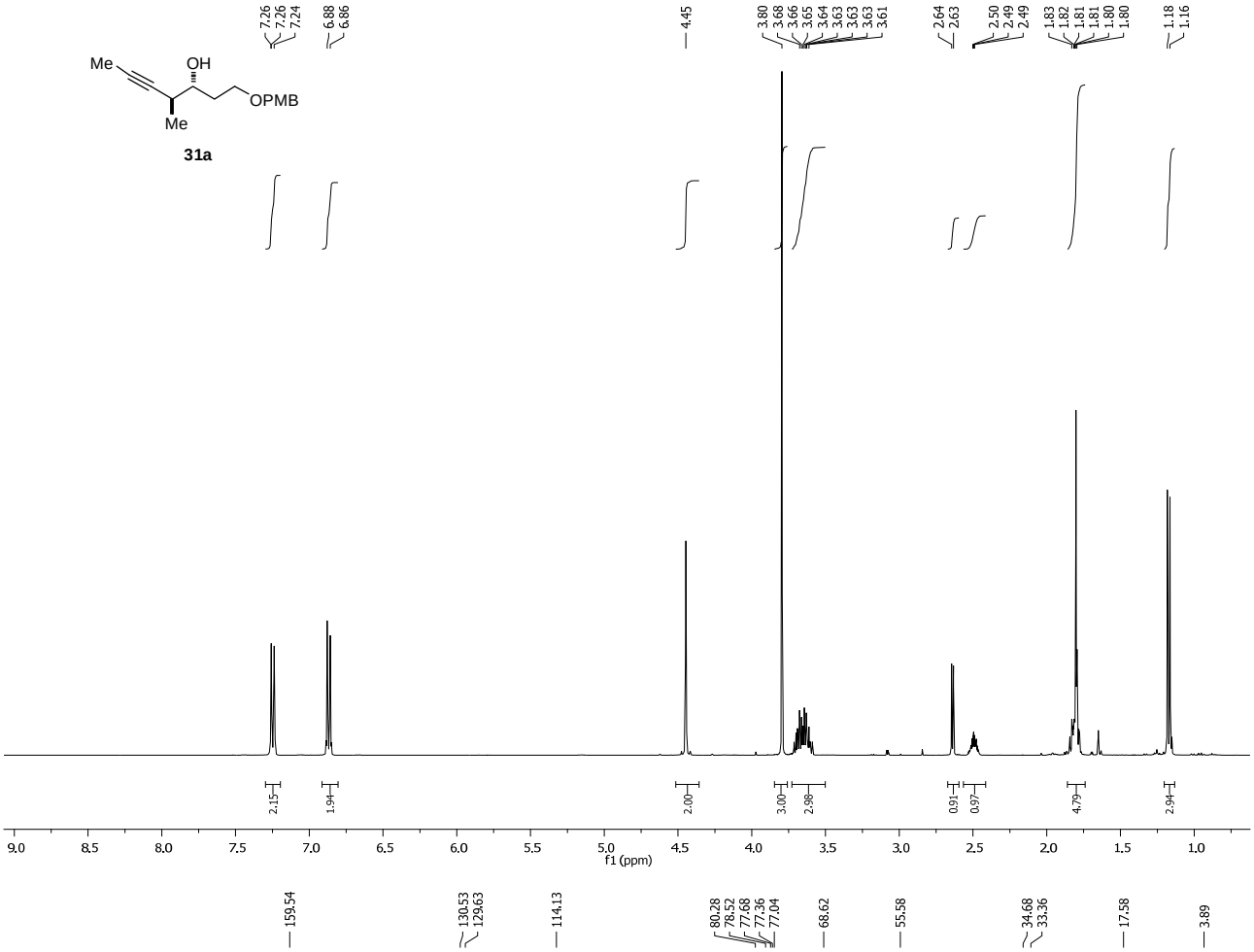
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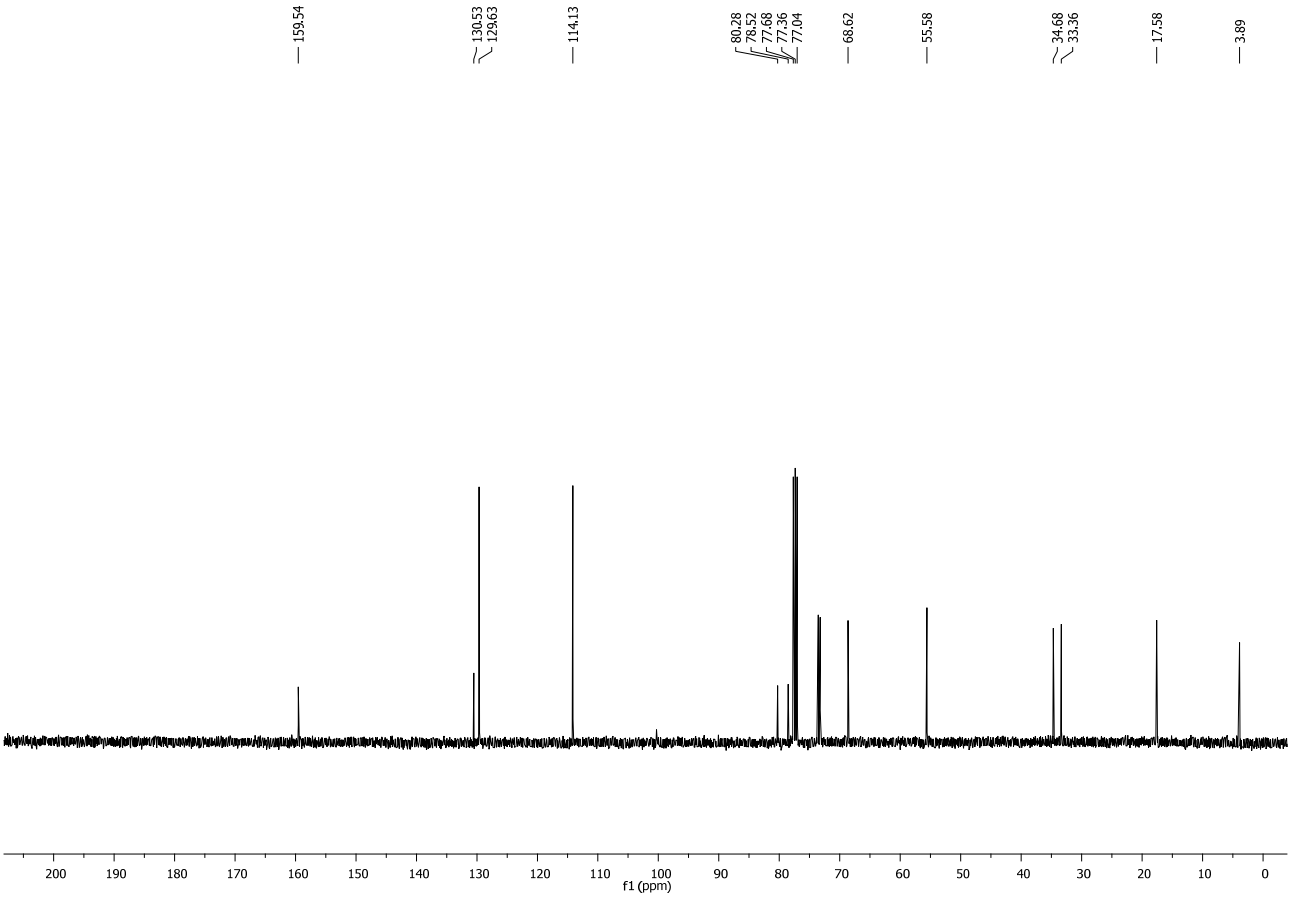
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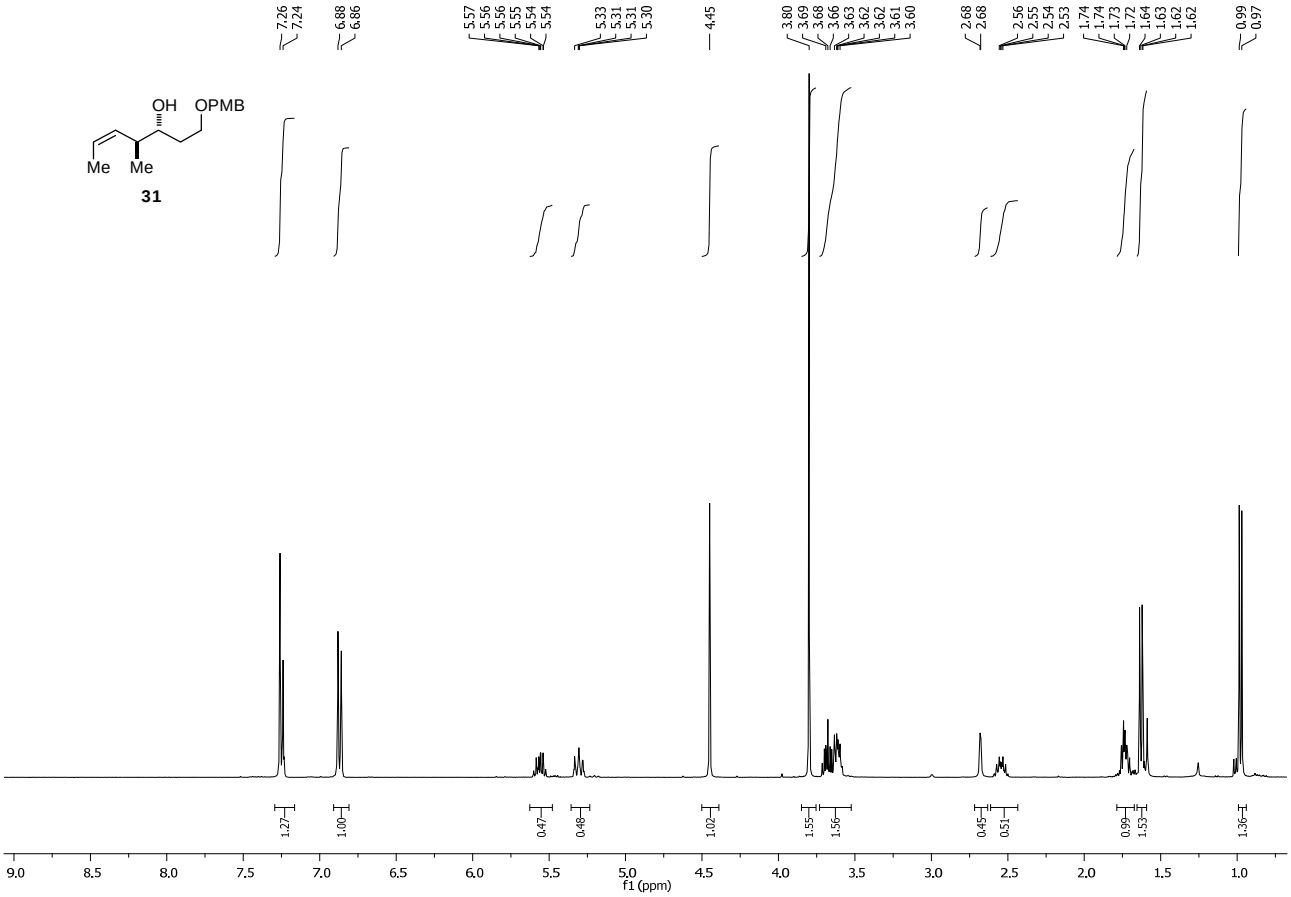
f1 (ppm)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2.54
2.53
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1.74
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1.64
1.63
1.62
1.62
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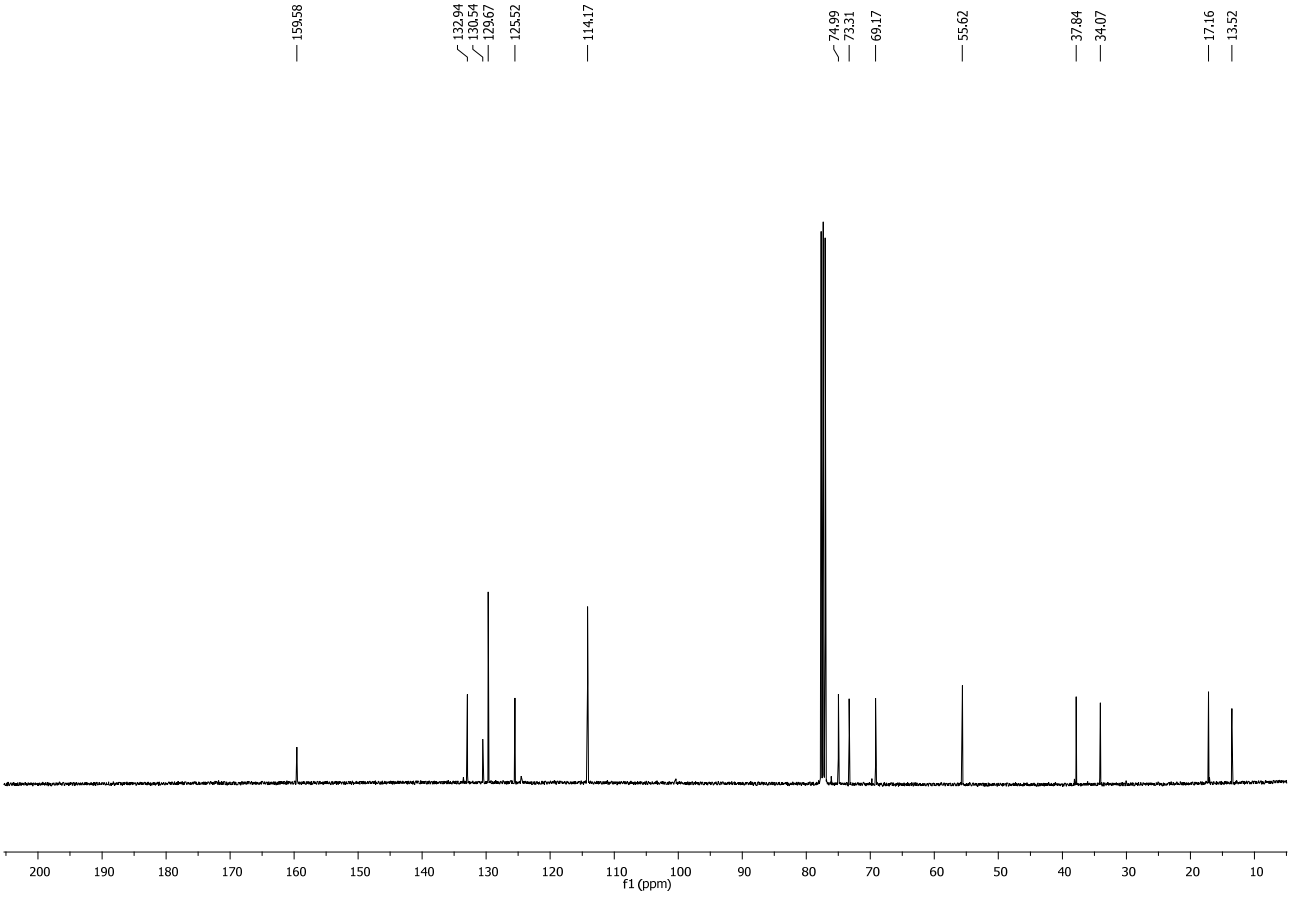
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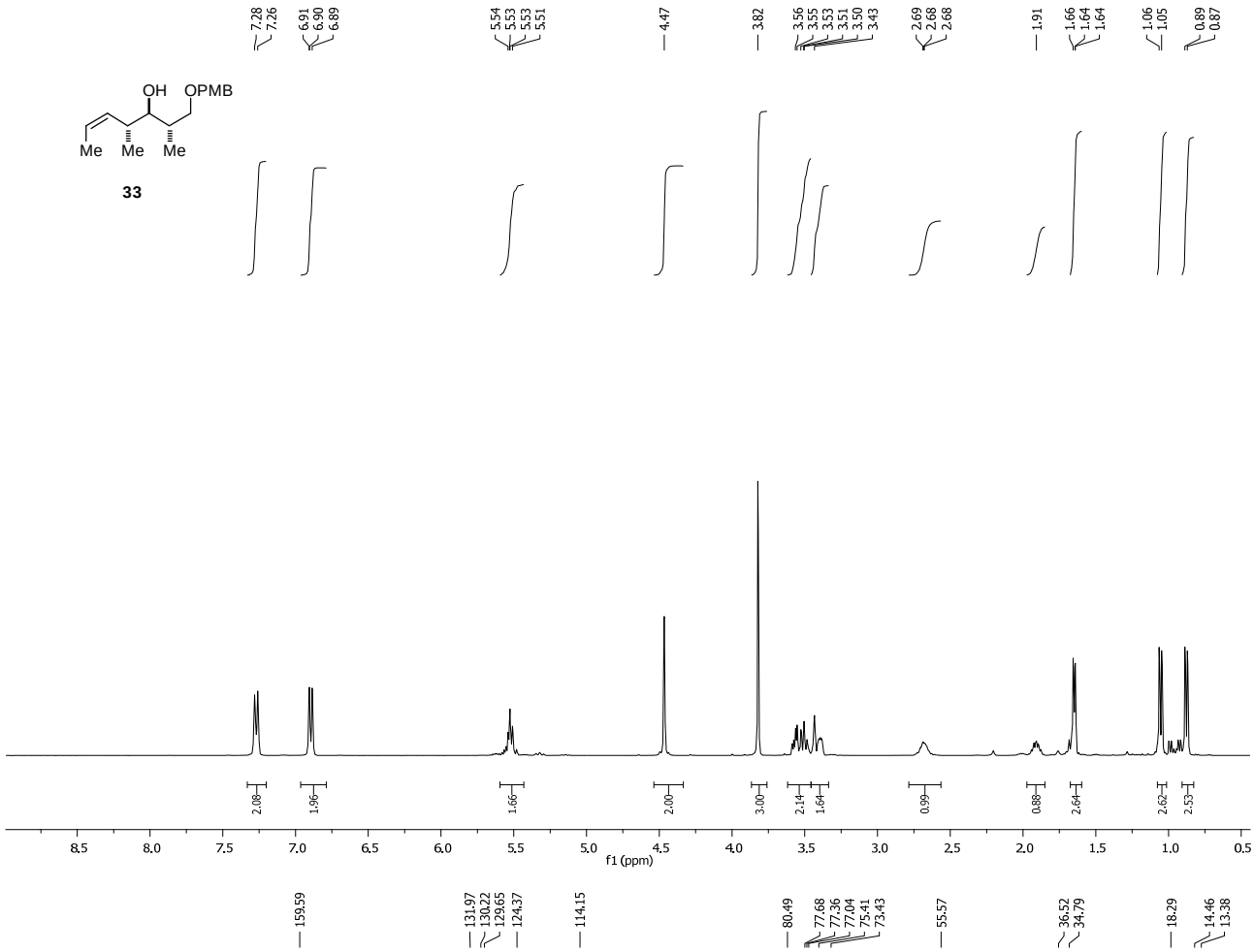
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OPMB
Me
Me
Me
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1.96
1.66
2.00
3.00
2.14
1.64
0.99
0.88
2.64
2.62
2.53
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
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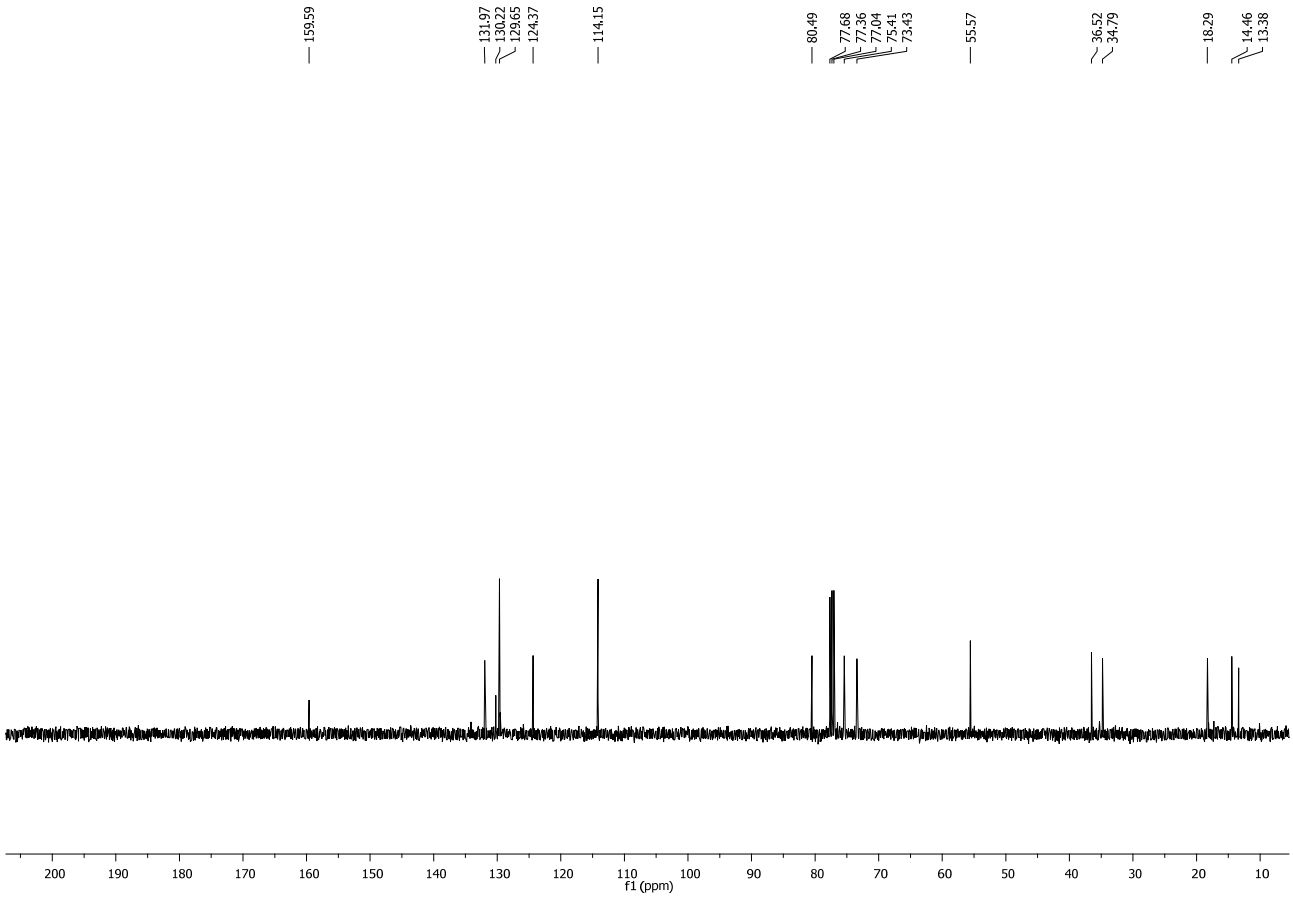
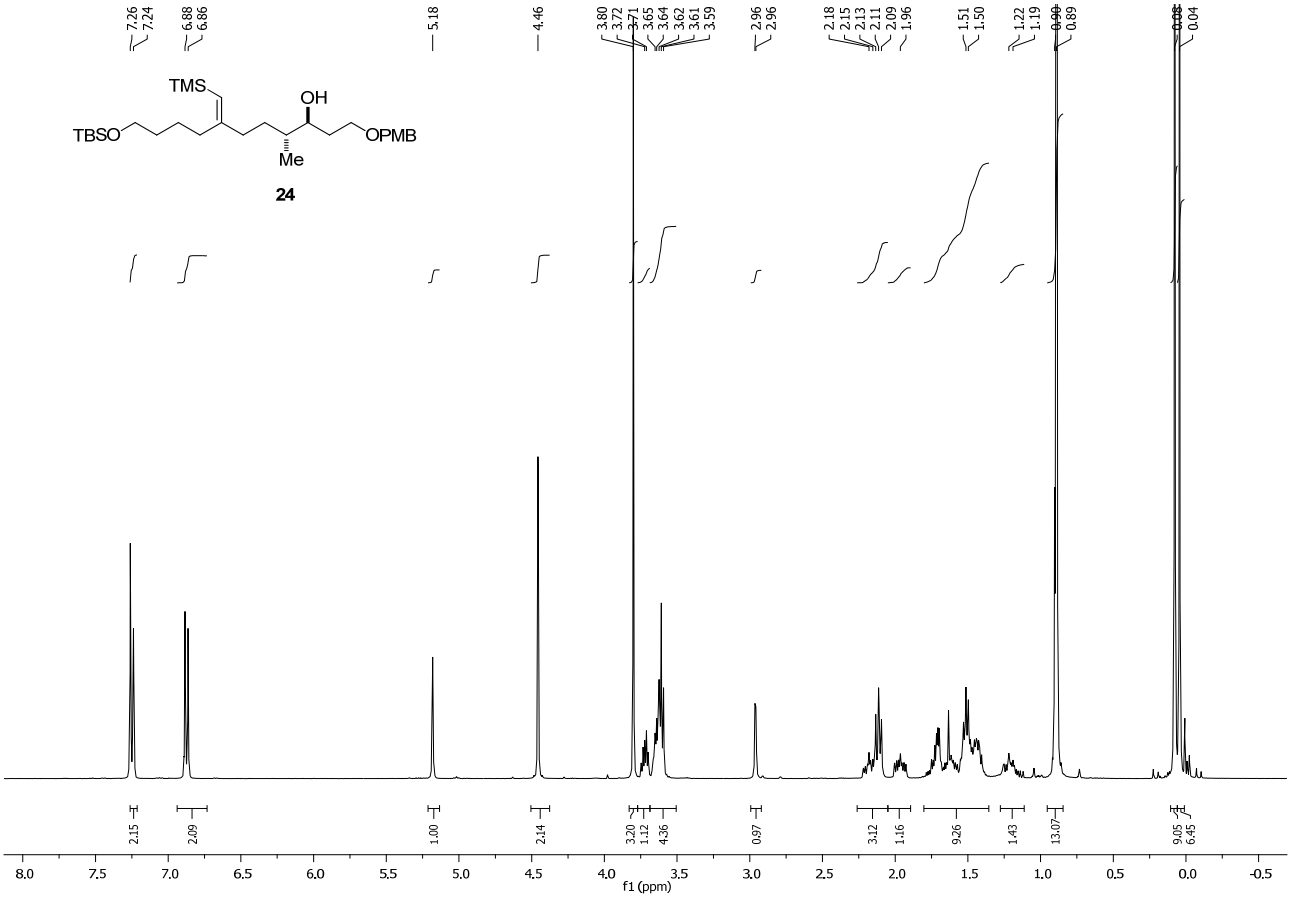
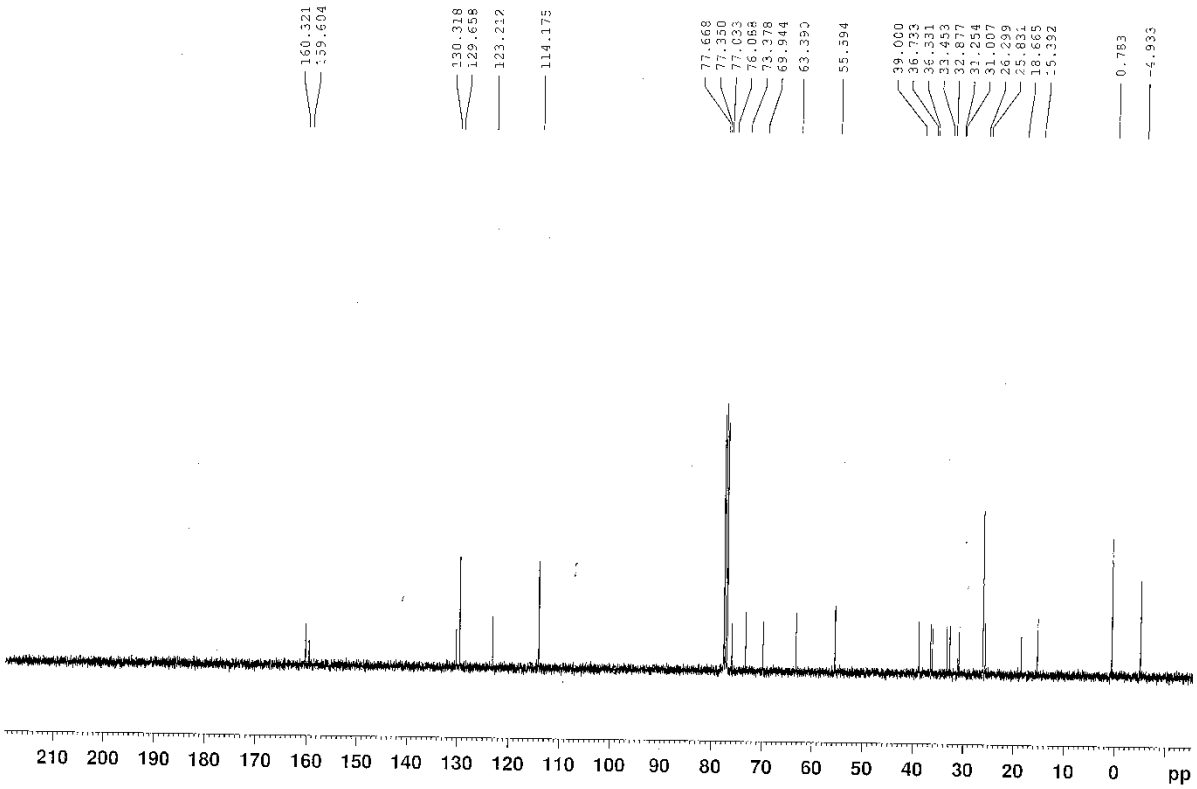
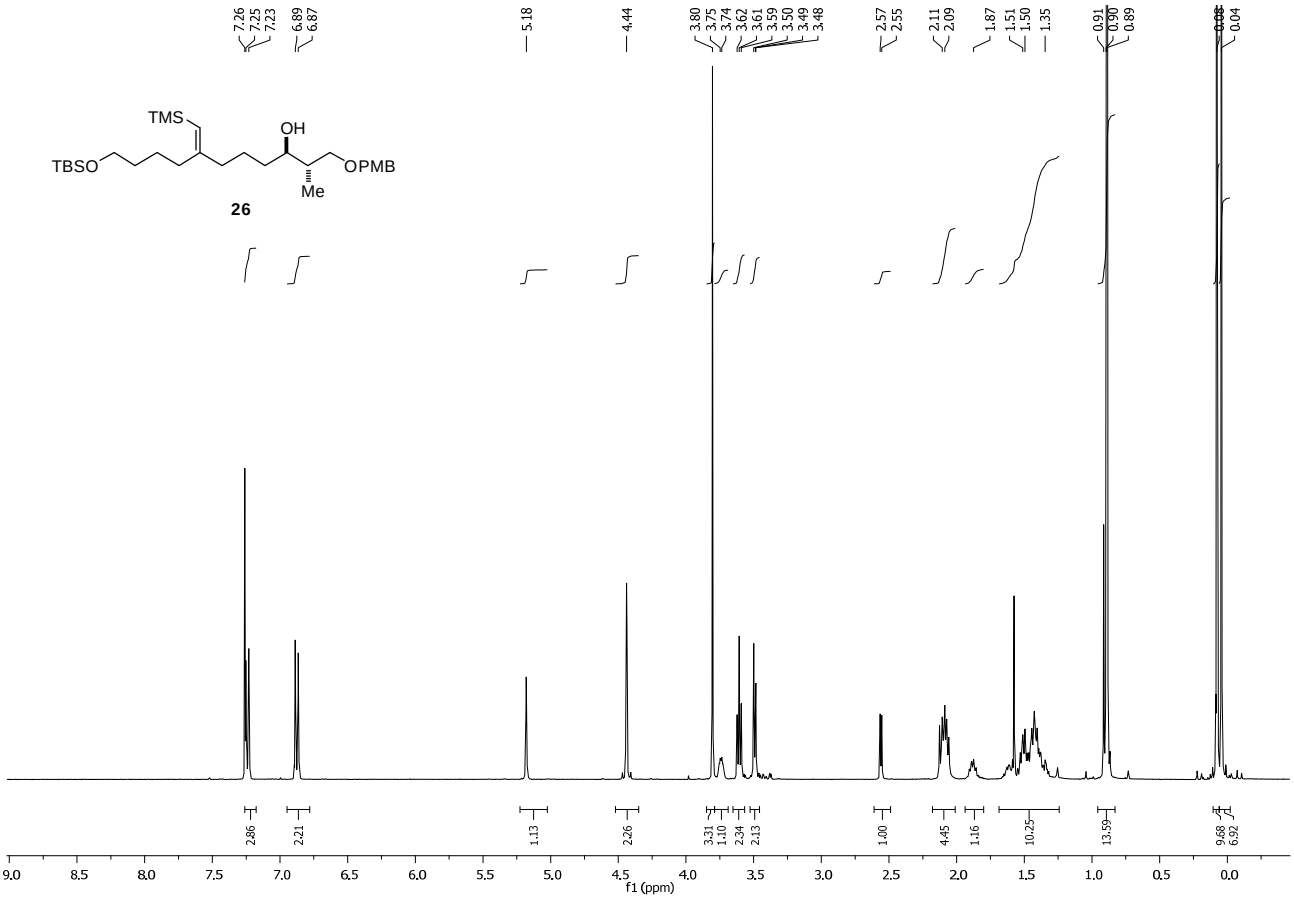
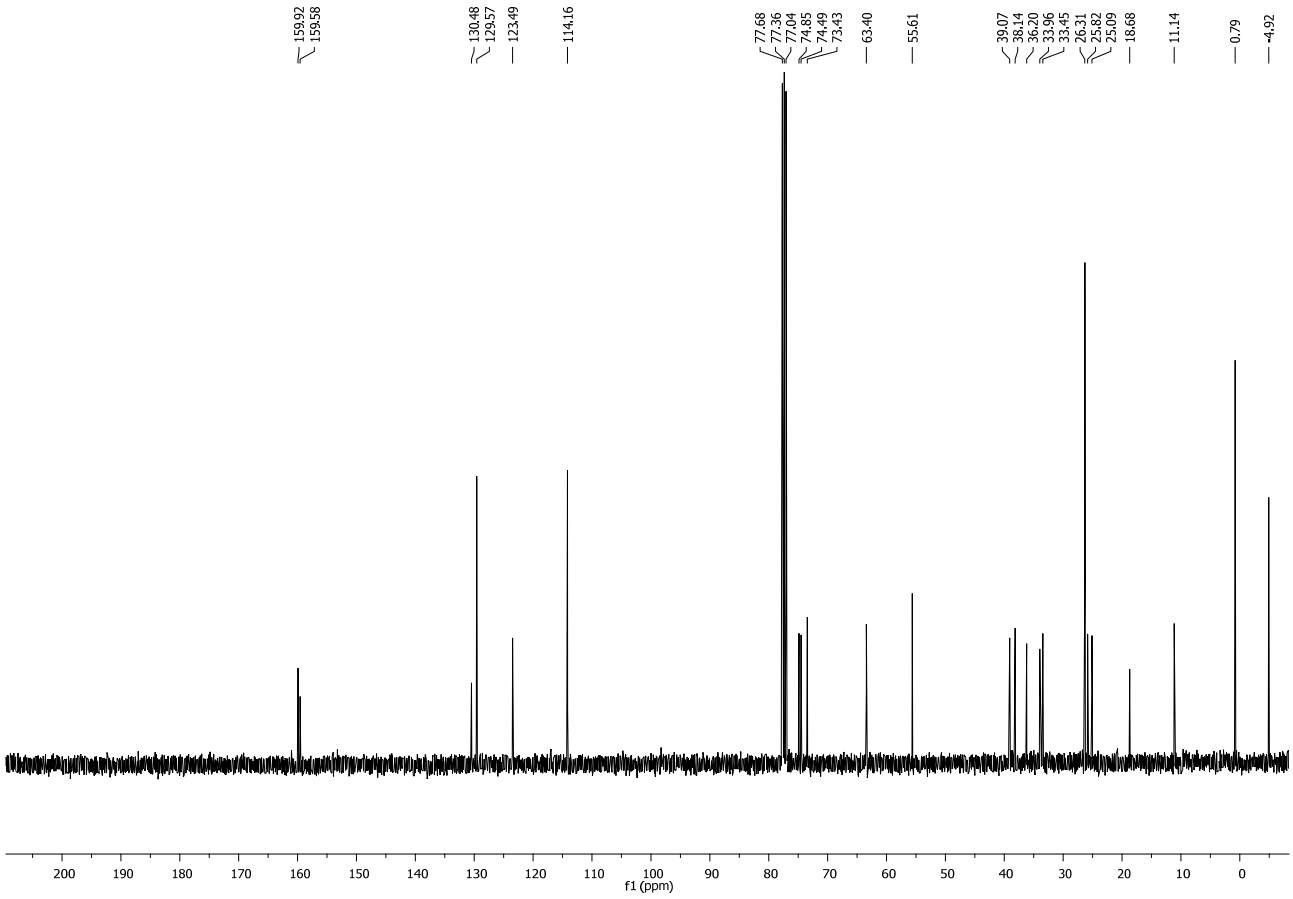
1.5
1.0
0.5
f1 (ppm)

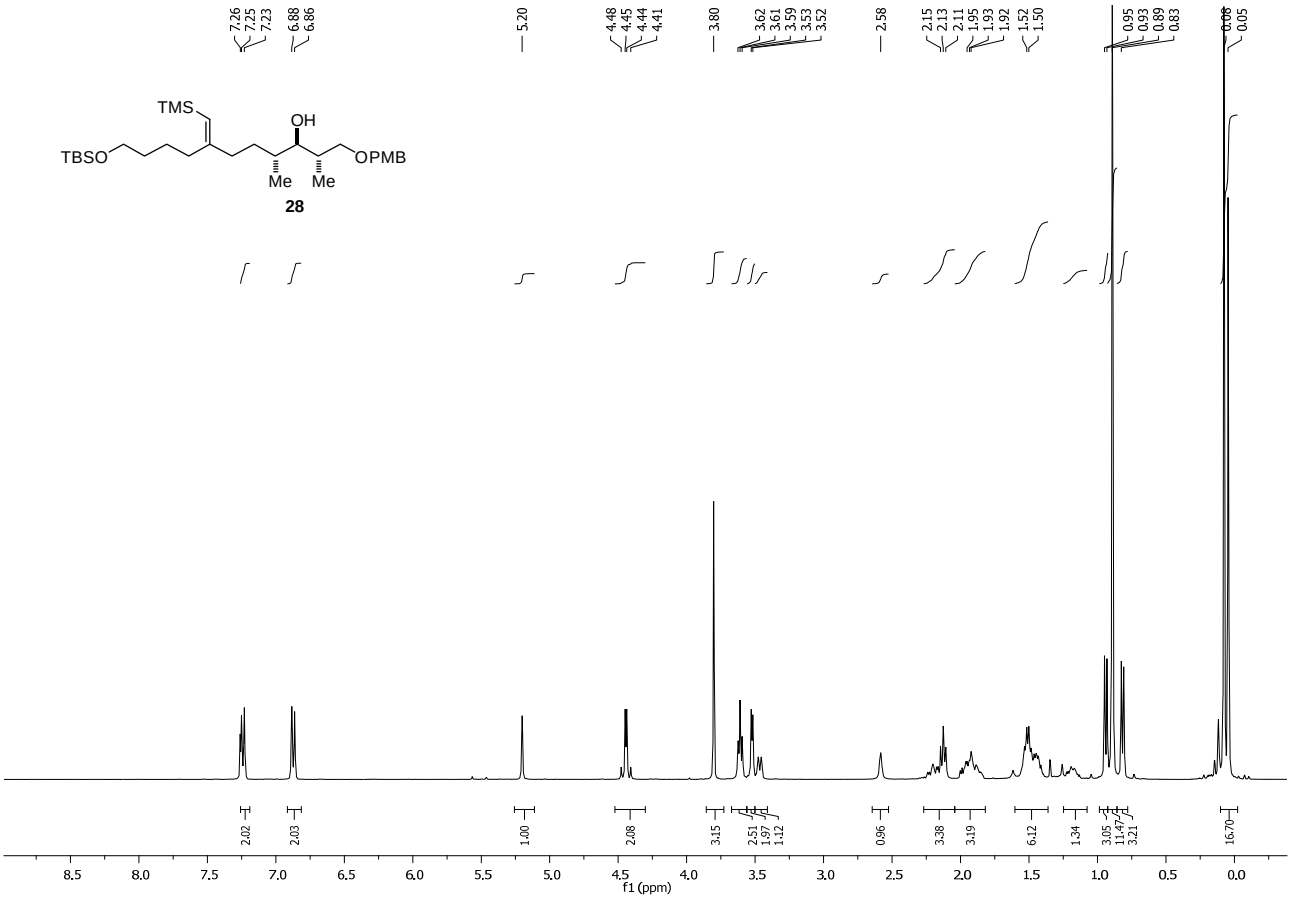

159.59
131.97
130.22
129.65
124.37
114.15
80.49
77.68
77.36
77.04
75.41
73.43
55.57
36.52
34.79
18.29
14.46
13.38
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

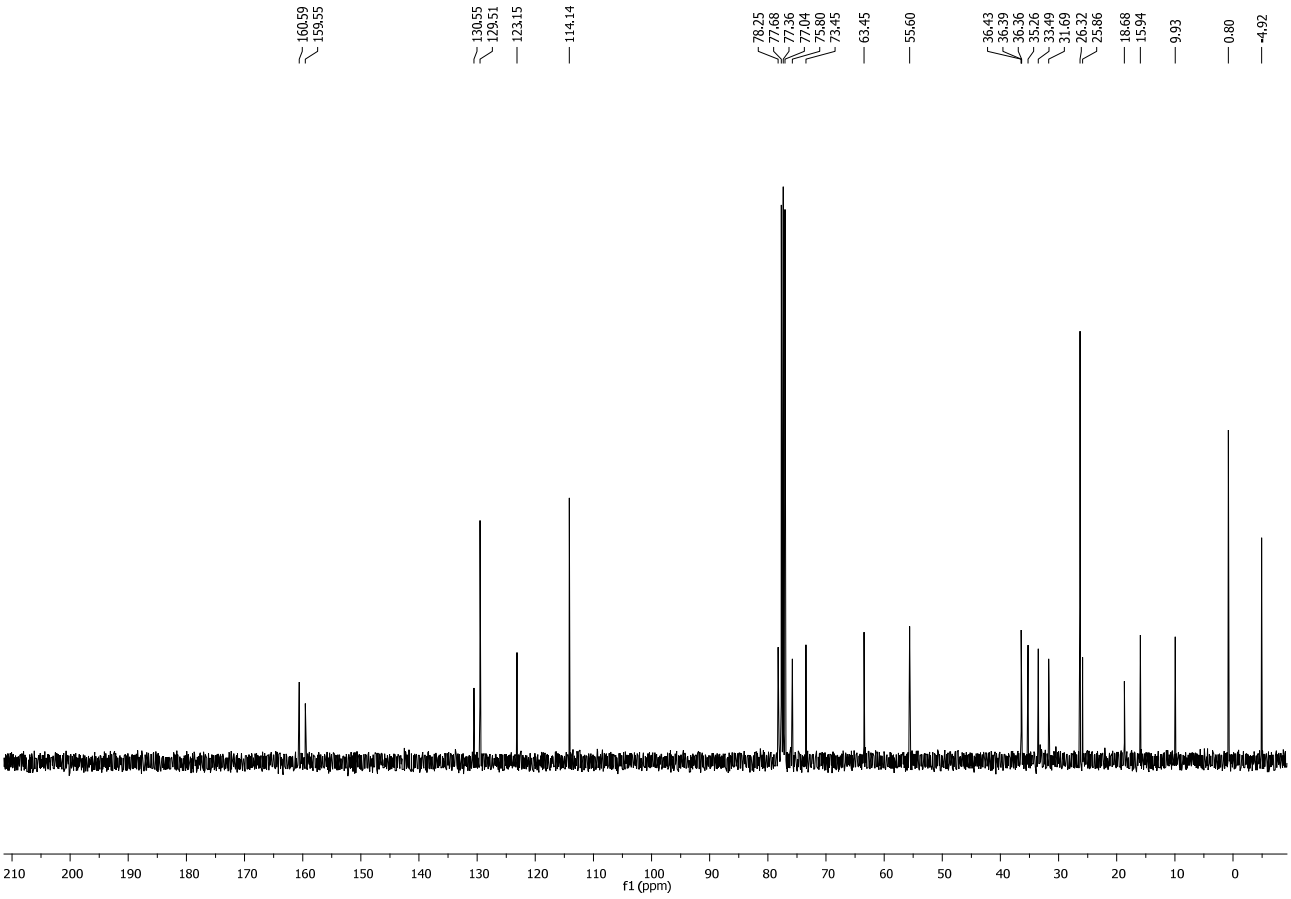

TMS
OH
TBSO
OPMB
Me
24
f1 (ppm)

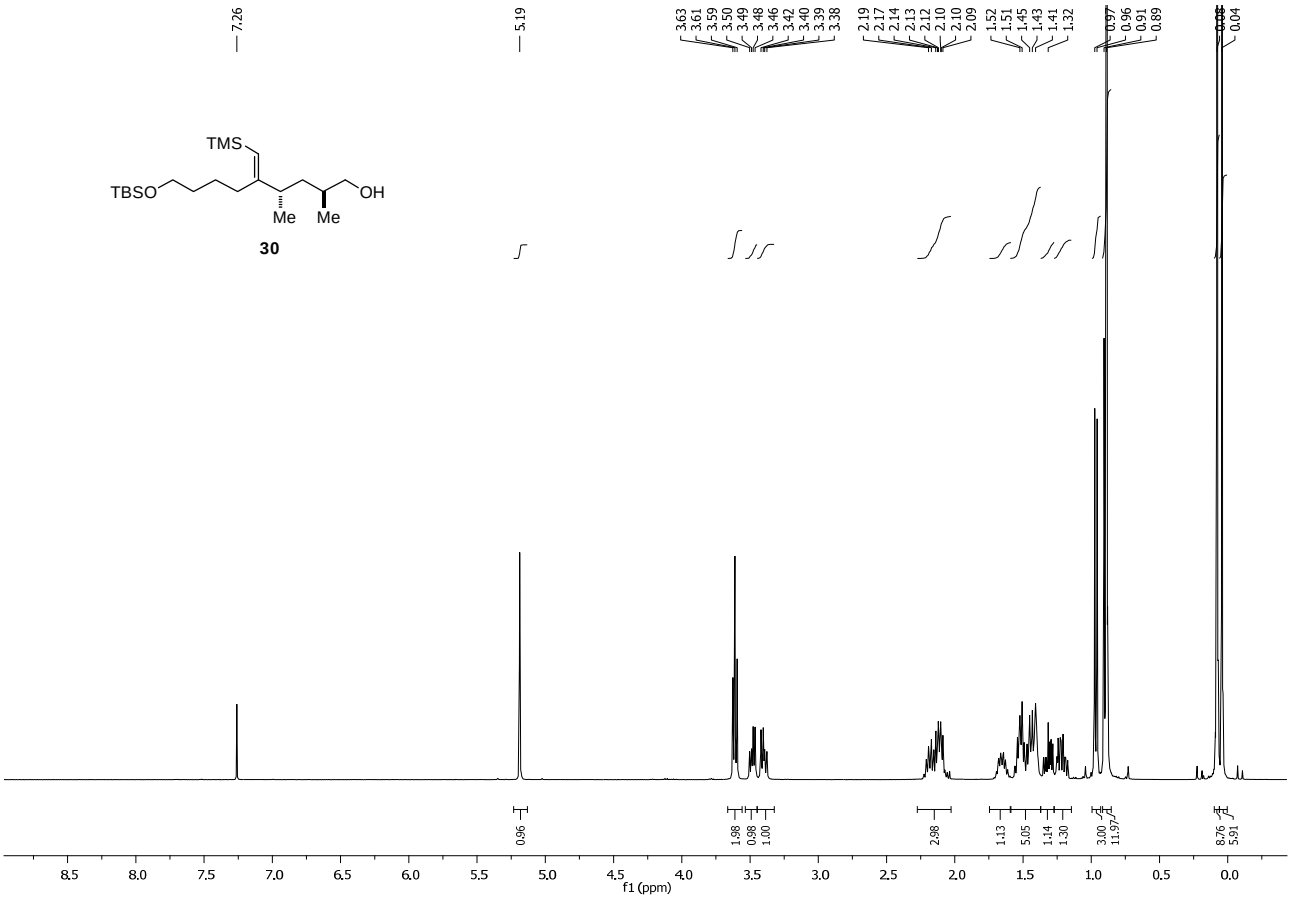


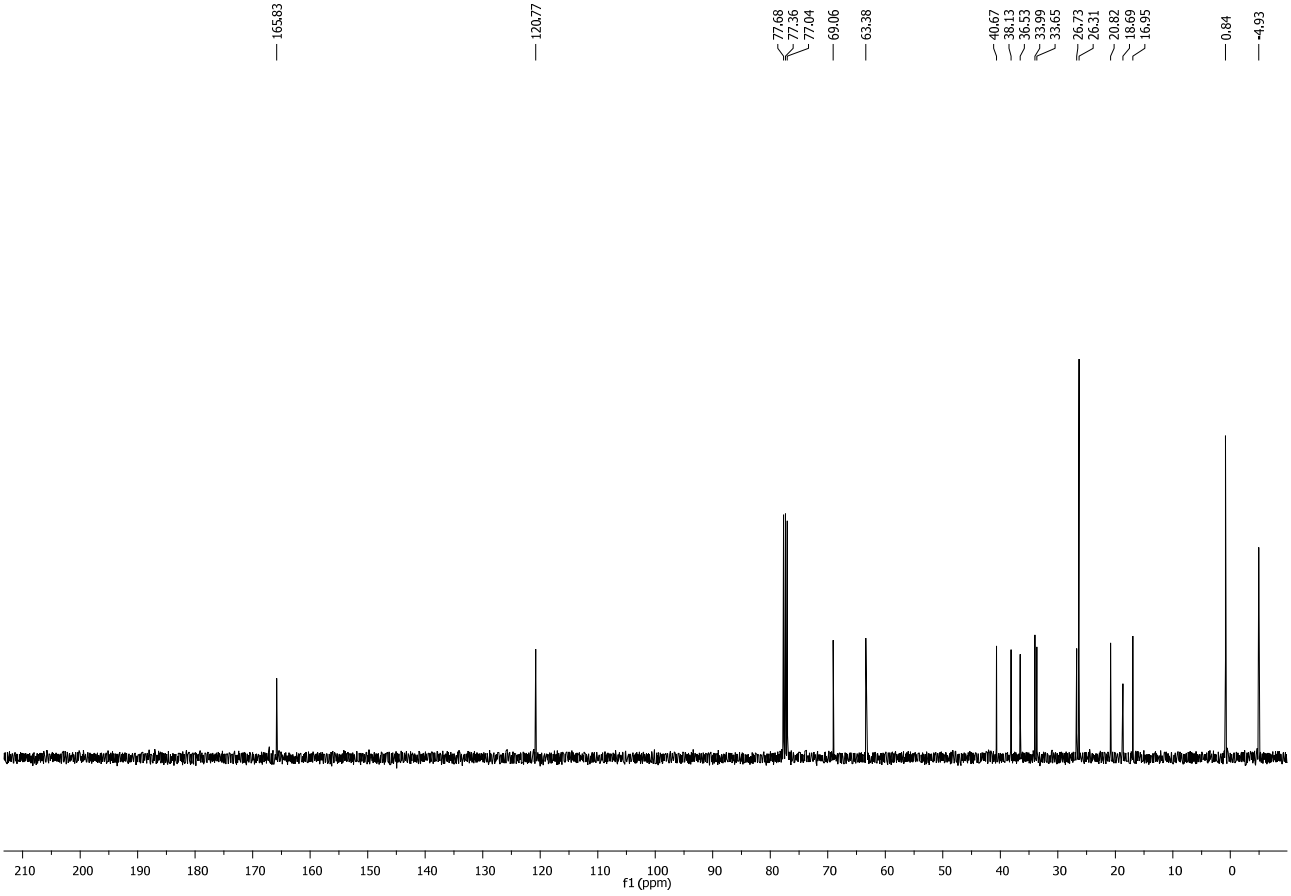

TMS
OH
TBSO
OPMB
Me
26
f1 (ppm)

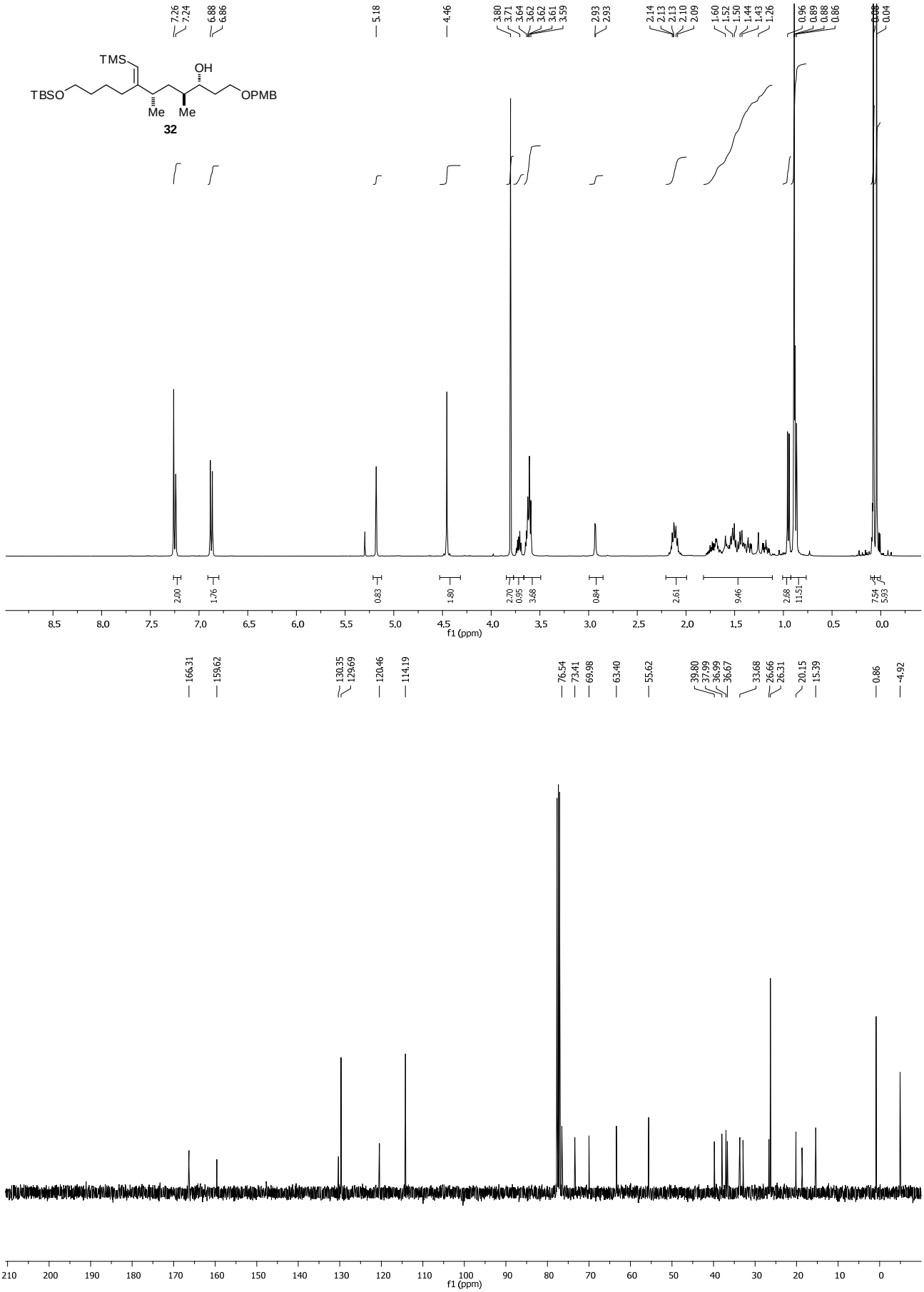

f1 (ppm)

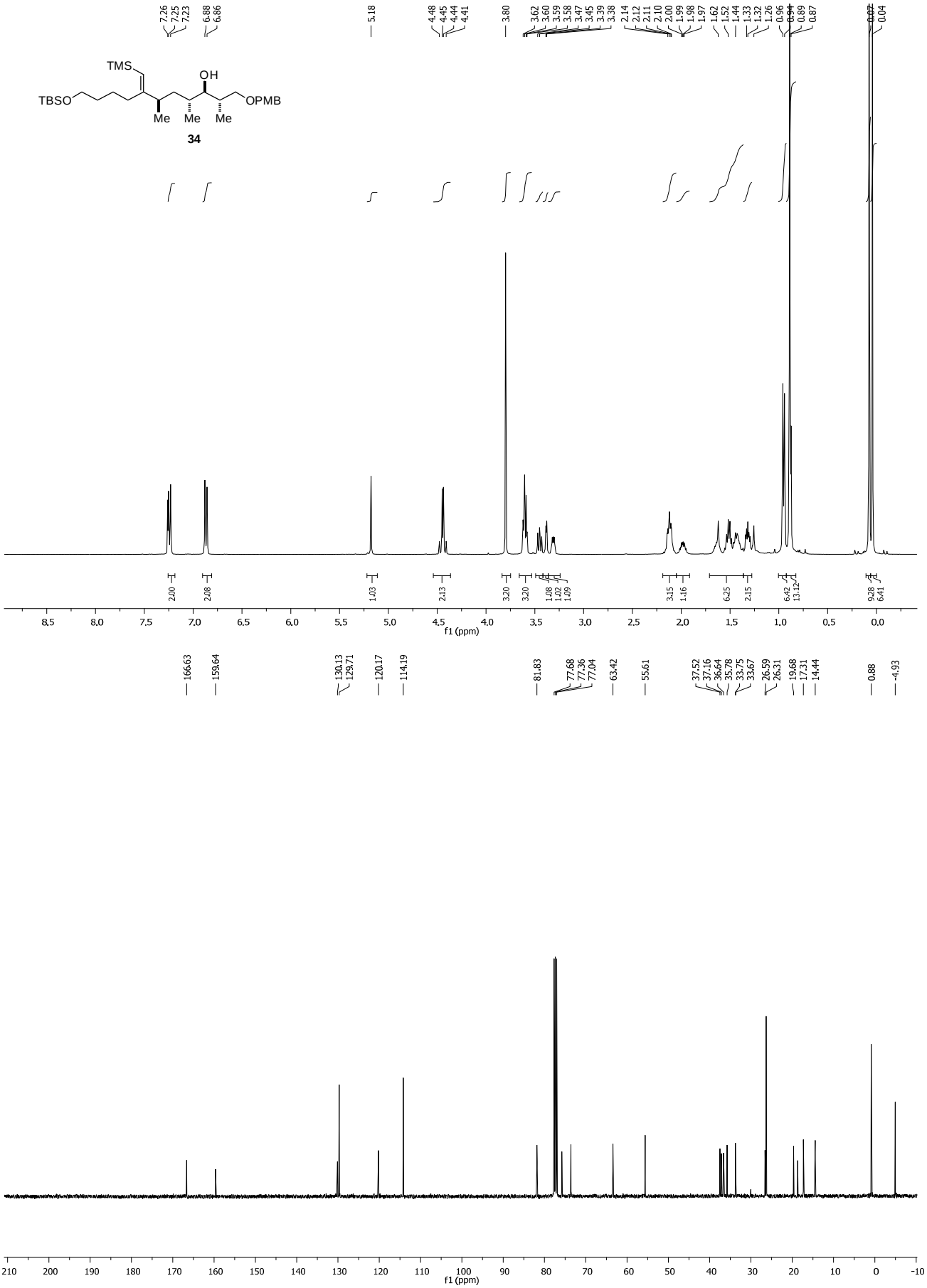

TMS
OH
TBSO
OPMB
Me
Me
28
f1 (ppm)

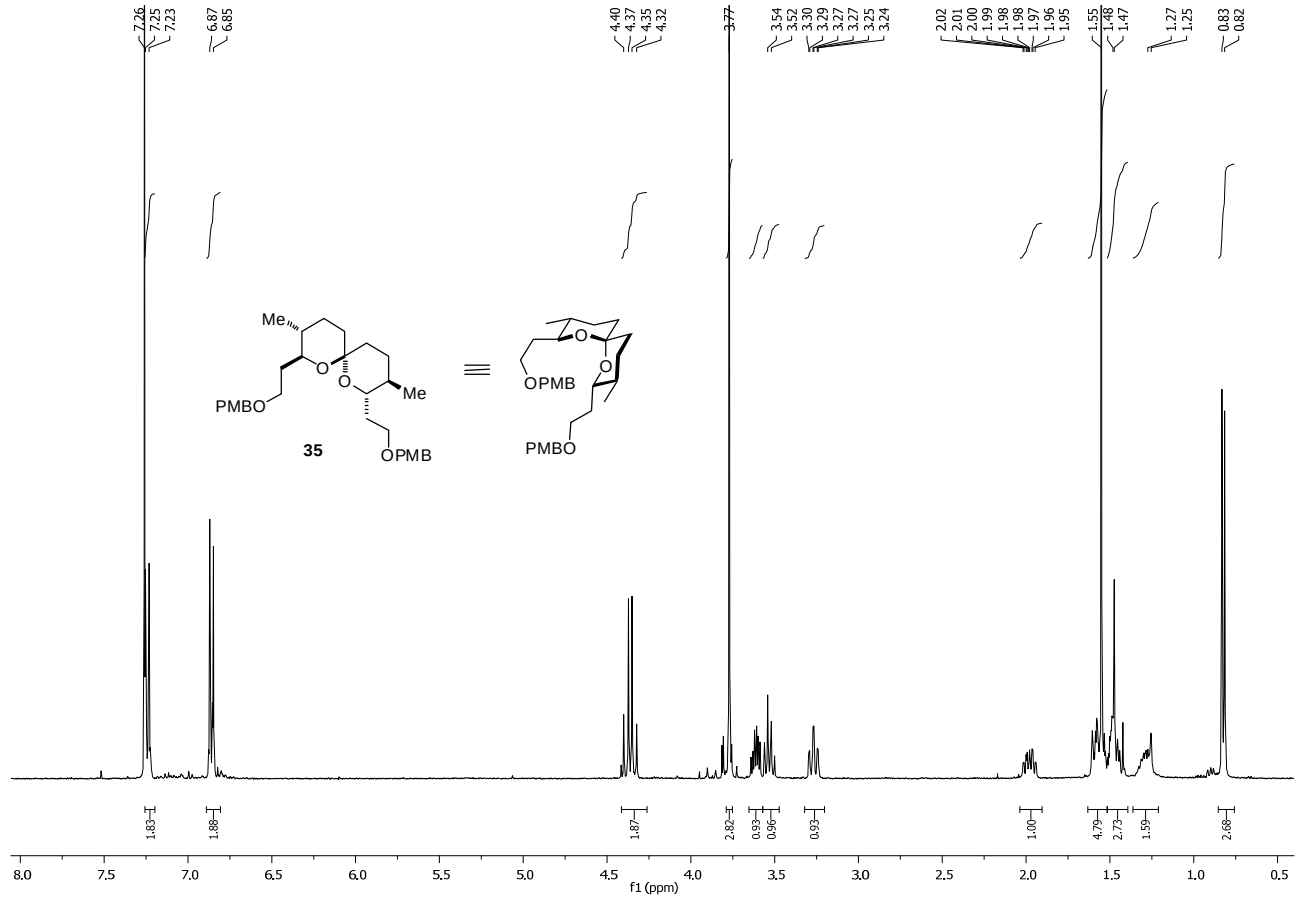

f1 (ppm)

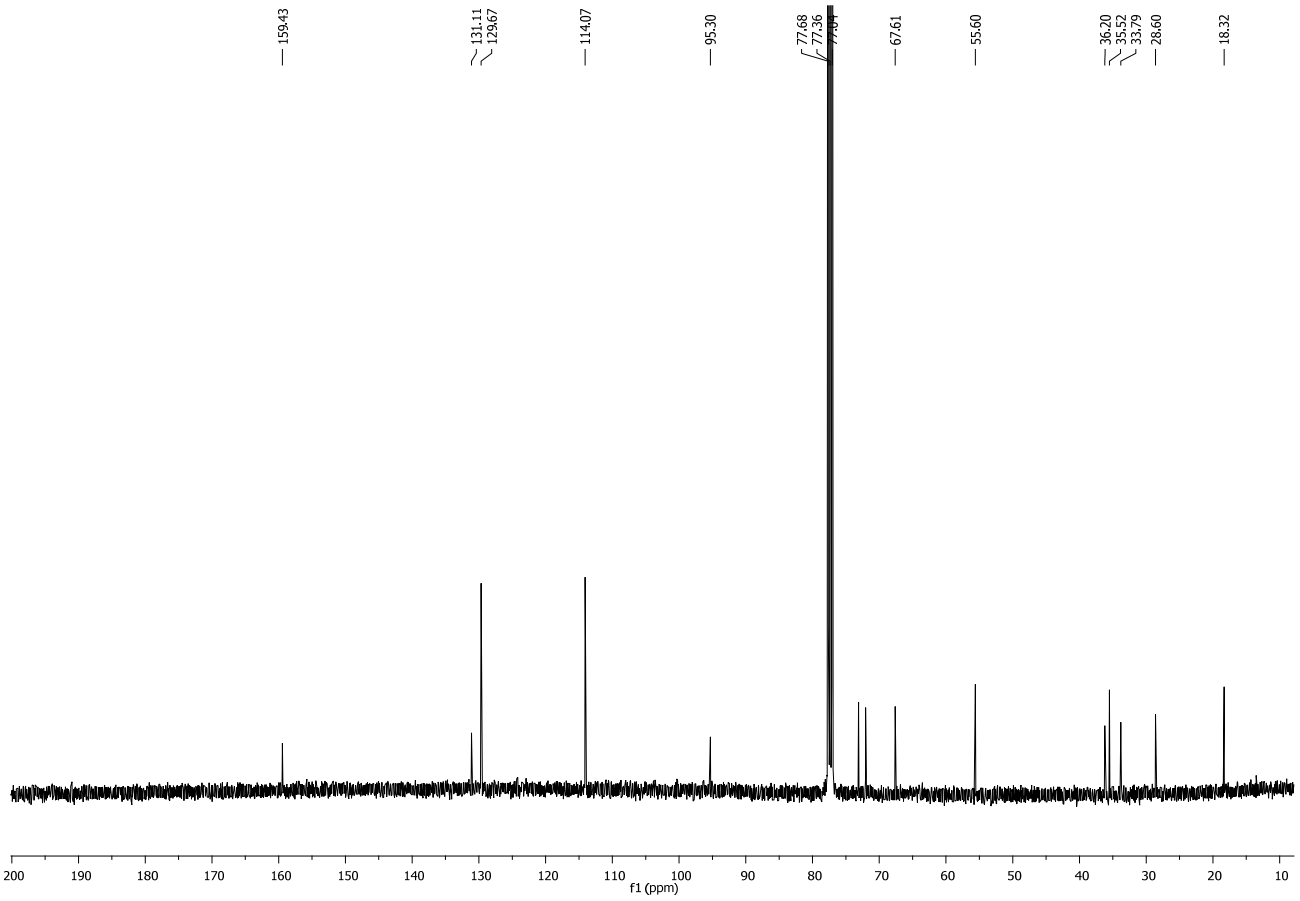

7.26
5.19
3.63
3.61
3.59
3.50
3.49
3.48
3.46
3.42
3.40
3.39
3.38
2.19
2.17
2.14
2.13
2.12
2.10
2.10
2.09
1.52
1.51
1.45
1.43
1.41
1.32
0.97
0.96
0.91
0.89
0.08
0.04
TMS
TBSO
OH
Me
Me
30
0.96
1.98
0.98
1.00
2.98
1.13
5.05
1.14
1.30
3.00
11.97
8.76
5.91
f1 (ppm)

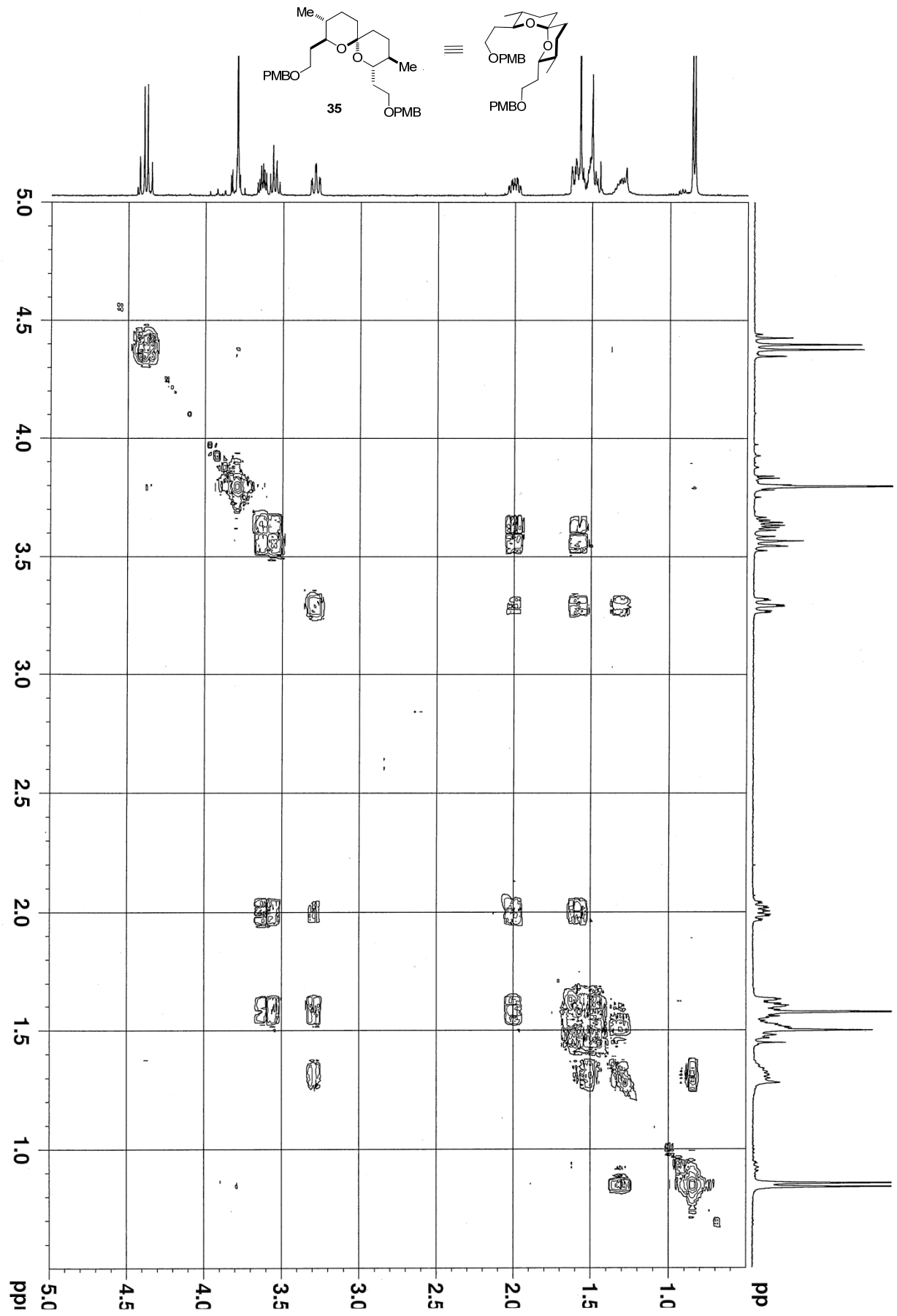

165.83
120.77
77.68
77.36
77.04
69.06
63.38
40.67
38.13
36.53
33.99
33.65
26.73
26.31
20.82
18.69
16.95
0.84
-4.93
f1 (ppm)

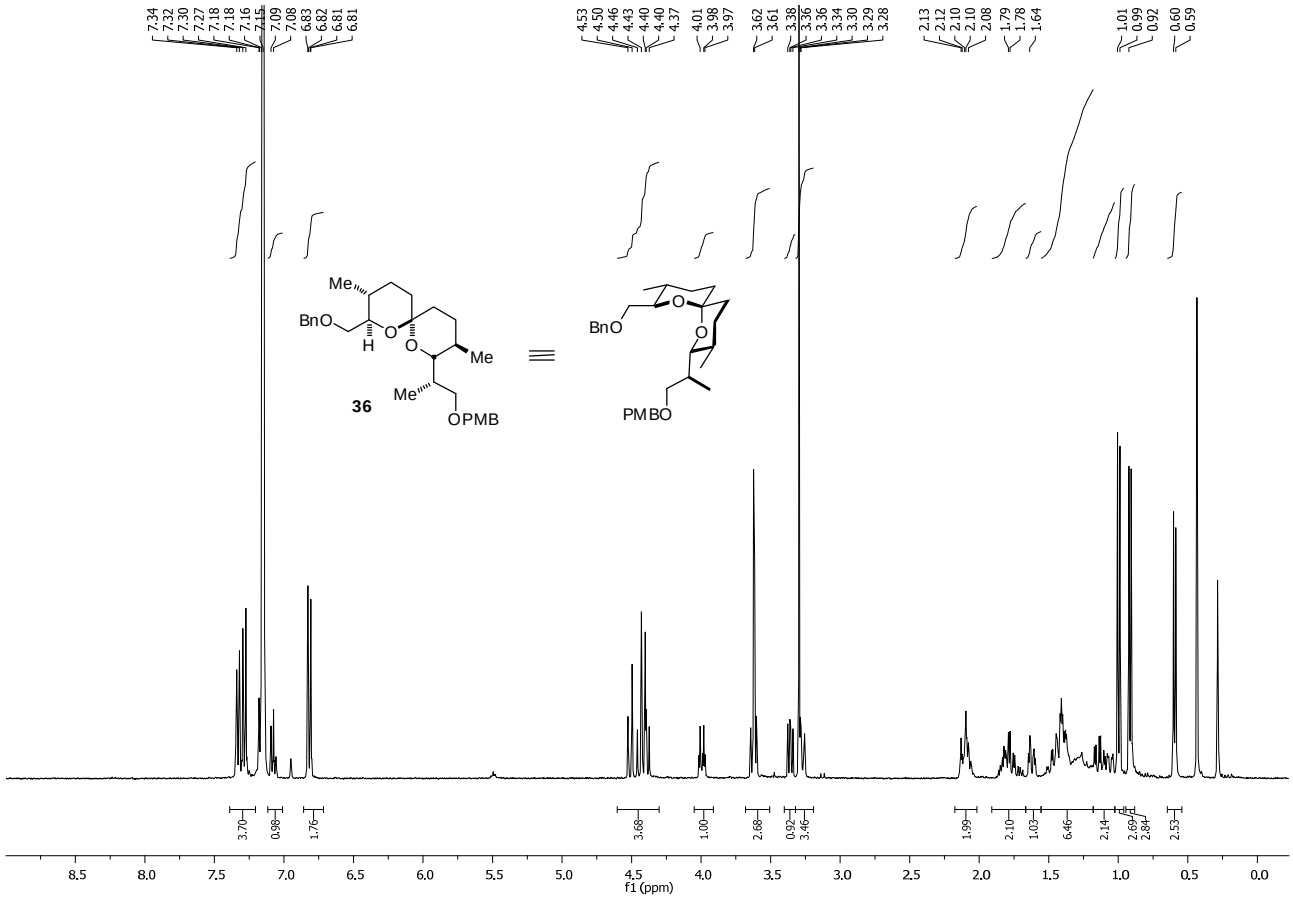

TMS
OH
TBSO
OPMB
Me
Me
32
f1 (ppm)
f1 (ppm)

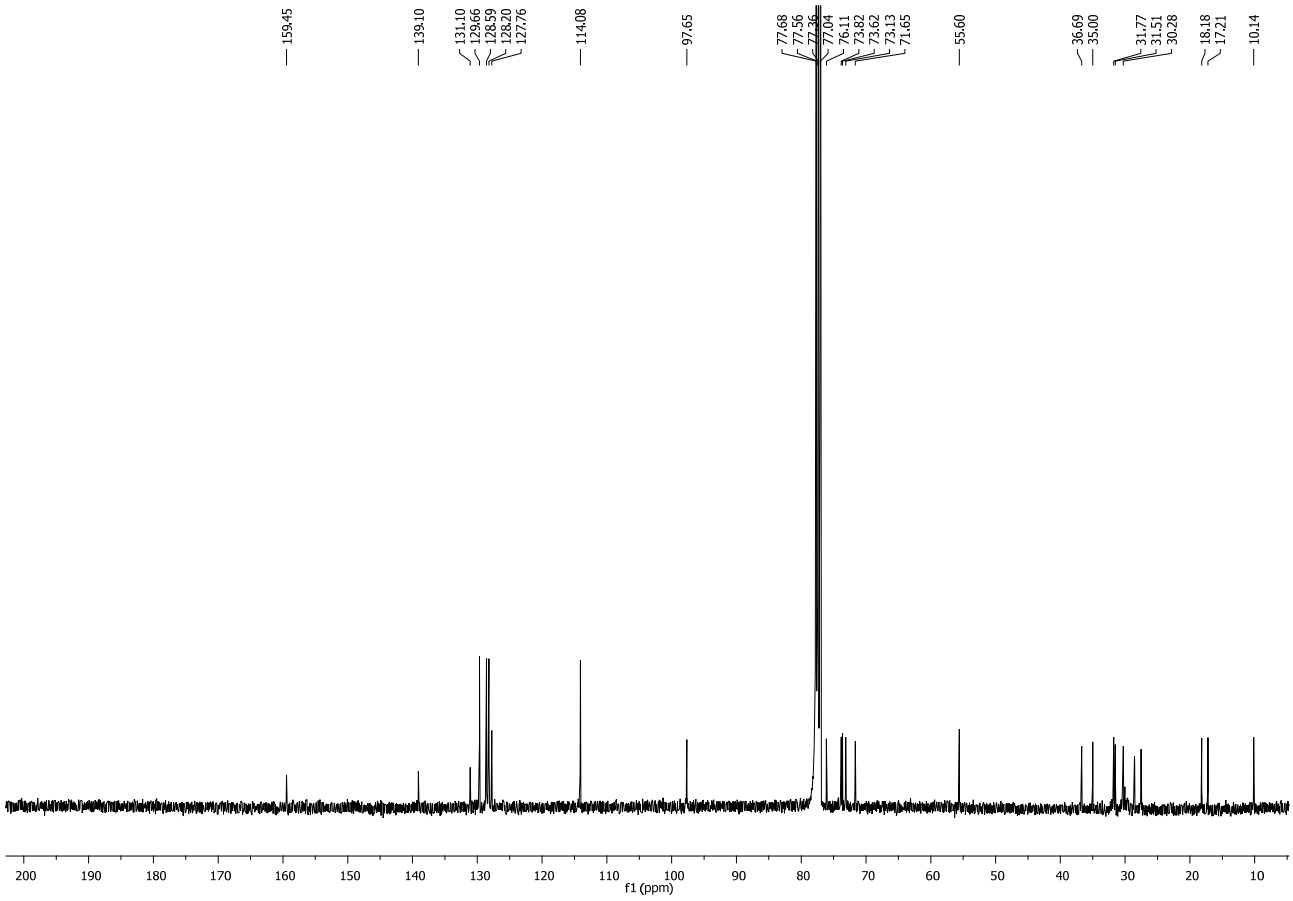

TMS
OH
TBSO
OPMB
Me
Me
Me
34
f1 (ppm)
f1 (ppm)

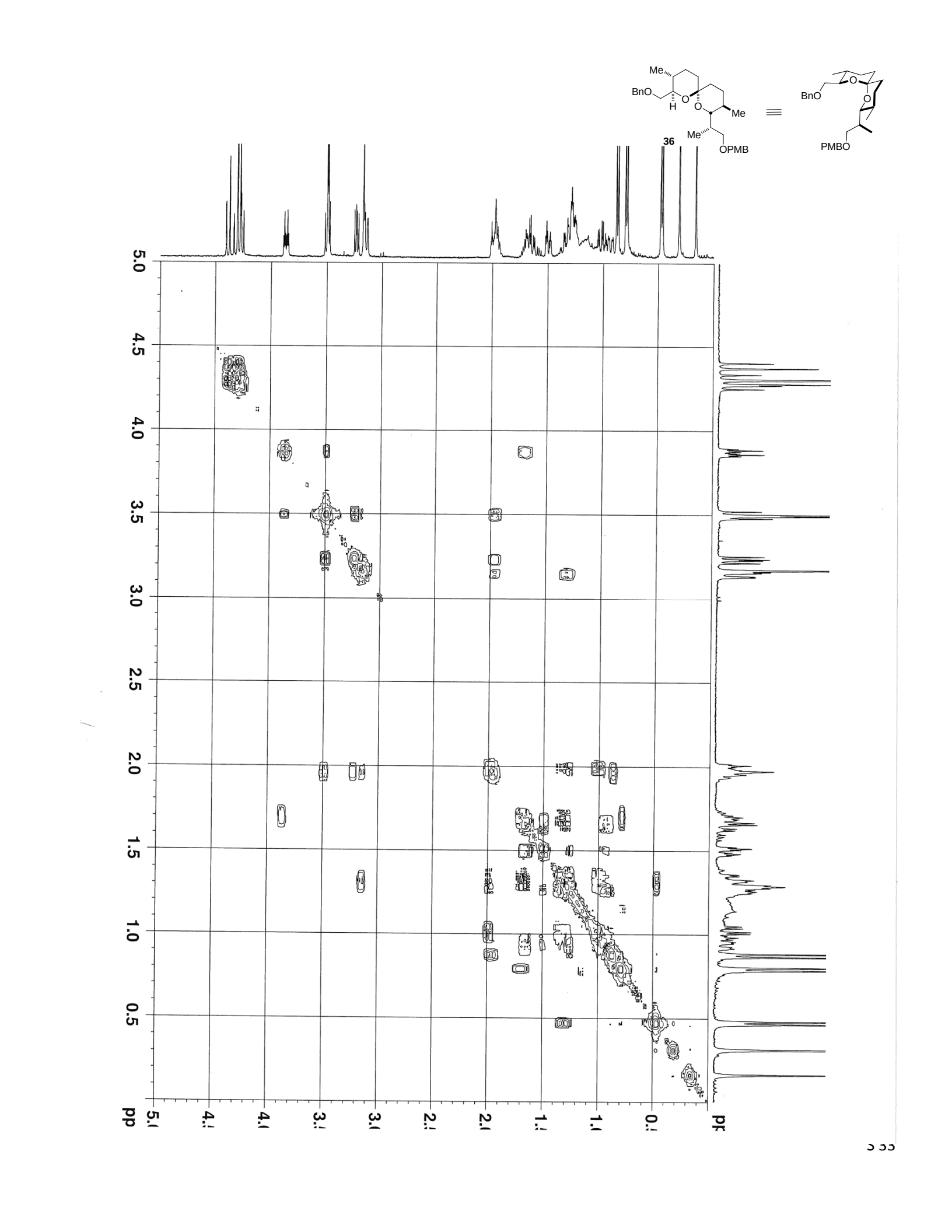

7.26
7.25
7.23
6.87
6.85
4.40
4.37
4.35
4.32
3.77
3.54
3.52
3.30
3.29
3.27
3.27
3.25
3.24
2.02
2.01
2.00
1.99
1.98
1.98
1.97
1.96
1.95
1.55
1.48
1.47
1.27
1.25
0.83
0.82
Me
PMBO
O
O
Me
OPMB
35
OPMB
PMBO
1.83
1.88
1.87
2.82
0.93
0.96
0.93
1.00
4.79
2.73
1.59
2.68
f1 (ppm)

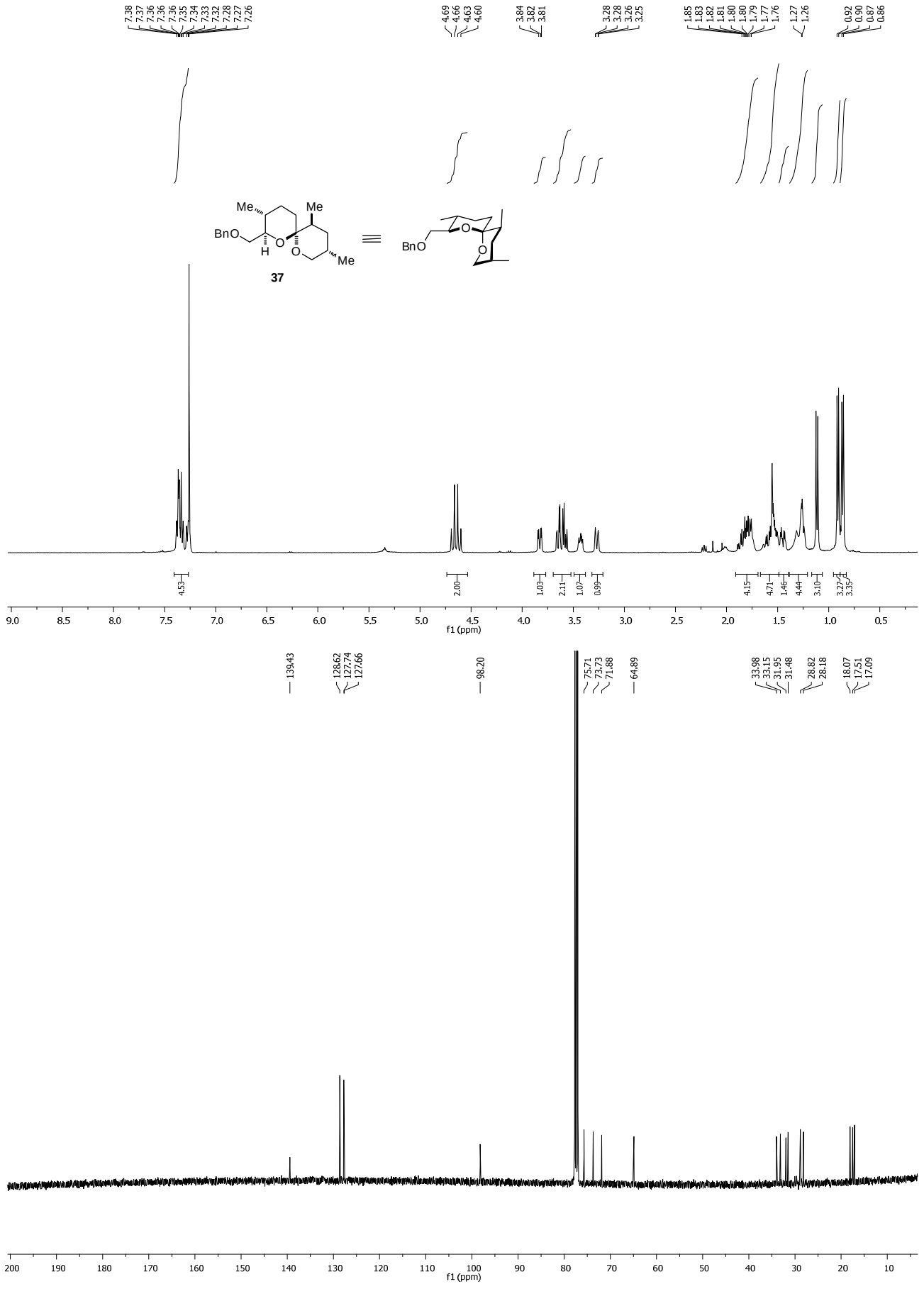

159.43
131.11
129.67
114.07
95.30
77.68
77.36
77.04
67.61
55.60
36.20
35.52
33.79
28.60
18.32
f1 (ppm)


Me
PMBO
O
O
Me
35
OPMB
OPMB
PMBO
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

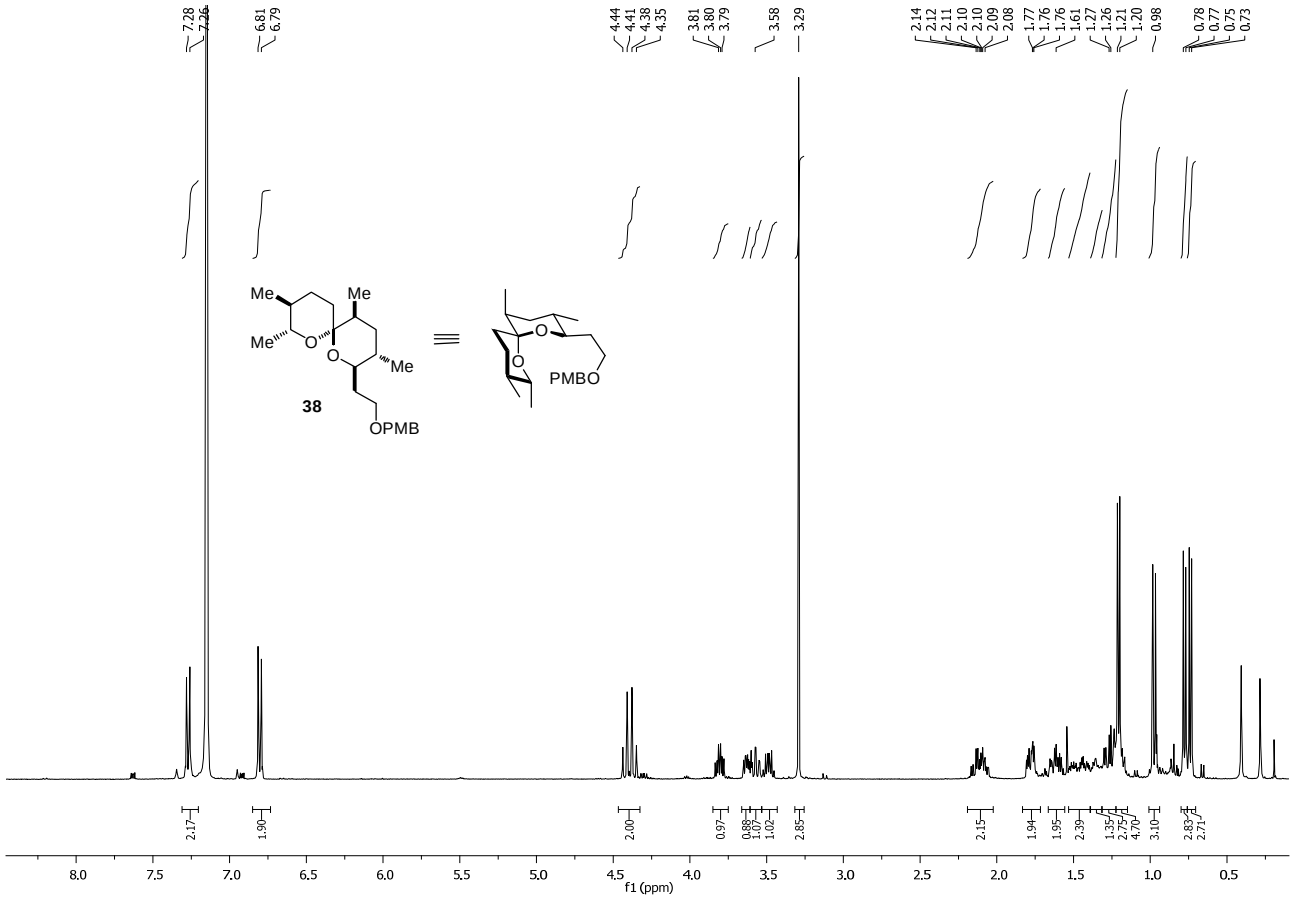

7.34
7.32
7.30
7.27
7.18
7.16
7.15
7.09
7.08
6.83
6.82
6.81
6.81
4.53
4.50
4.46
4.43
4.40
4.40
4.37
4.01
3.98
3.97
3.62
3.61
3.38
3.36
3.36
3.34
3.30
3.29
3.28
2.13
2.12
2.10
2.10
2.08
1.79
1.78
1.64
1.01
0.99
0.92
0.60
0.59
Me
BnO
O
H
O
Me
Me
OPMB
36
BnO
O
O
PMBO
3.70
0.98
1.76
3.68
1.00
2.68
0.92
3.46
1.99
2.10
1.03
6.46
2.14
2.69
2.84
2.53
f1 (ppm)


159.45
139.10
131.10
129.66
128.59
128.20
127.76
114.08
97.65
77.68
77.56
77.36
77.04
76.11
73.82
73.62
73.13
71.65
55.60
36.69
35.00
31.77
31.51
30.28
18.18
17.21
10.14
f1 (ppm)


Me
BnO
H
O
O
Me
Me
OPMB
36
BnO
O
O
PMBO
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


7.38 7.37 7.36 7.36 7.36 7.35 7.34 7.33 7.32 7.28 7.27 7.26
4.69 4.66 4.63 4.60
3.84 3.82 3.81
3.28 3.28 3.26 3.25
1.85 1.83 1.82 1.81 1.80 1.80 1.79 1.77 1.76
1.27 1.26
0.92 0.90 0.87 0.86
Me
Me
BnO
H
O
O
Me
BnO
O
O
37
4.53
2.00
1.03
2.11
1.07
0.99
4.15
4.71
1.46
4.44
3.10
3.27
3.35
f1 (ppm)
139.43
128.62
127.74
127.66
98.20
75.71
73.73
71.88
64.89
33.98
33.15
31.95
31.48
28.82
28.18
18.07
17.51
17.09
f1 (ppm)

Me
Me
BnO
H
O
O
Me
37
BnO
O
O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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7.26
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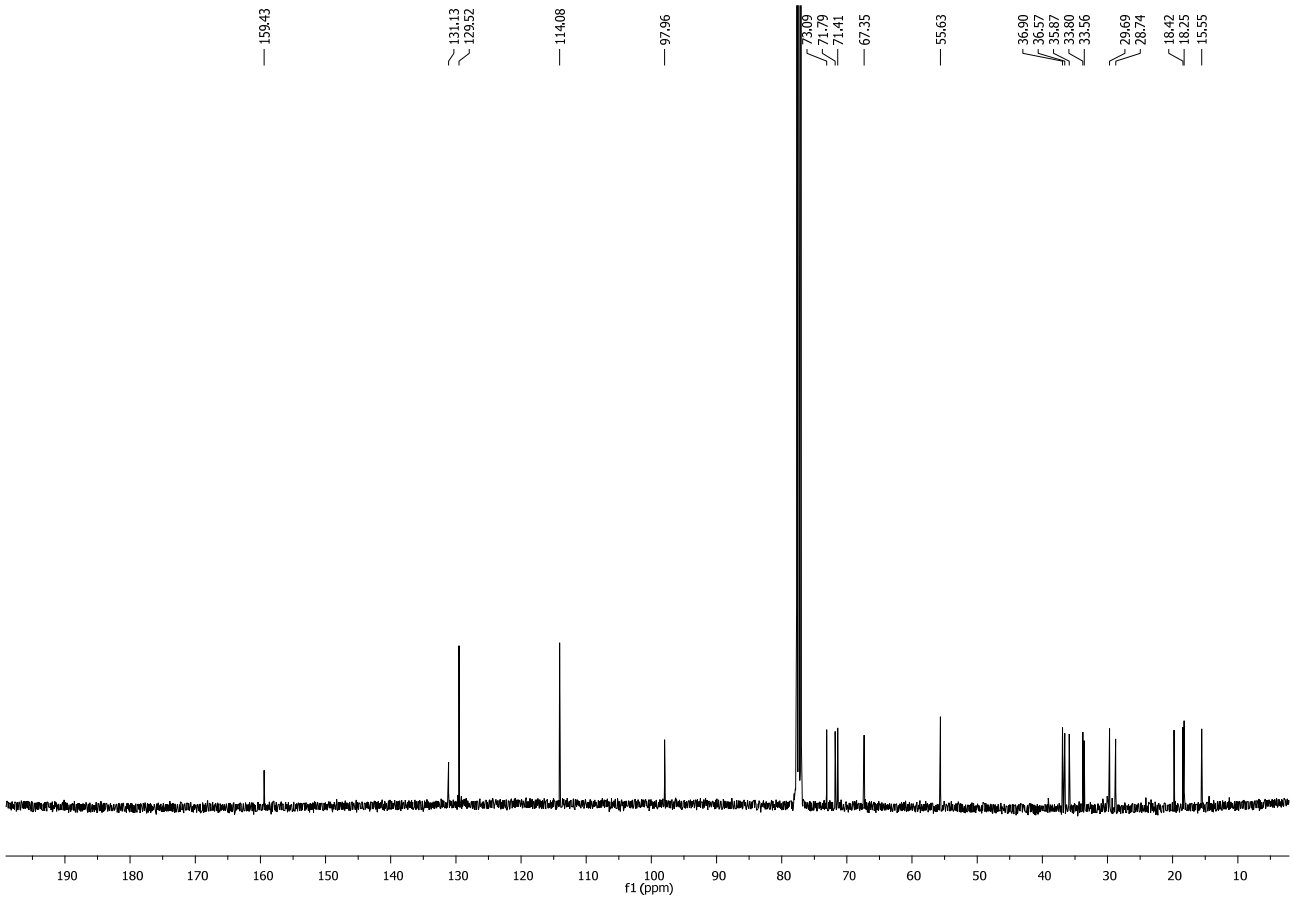
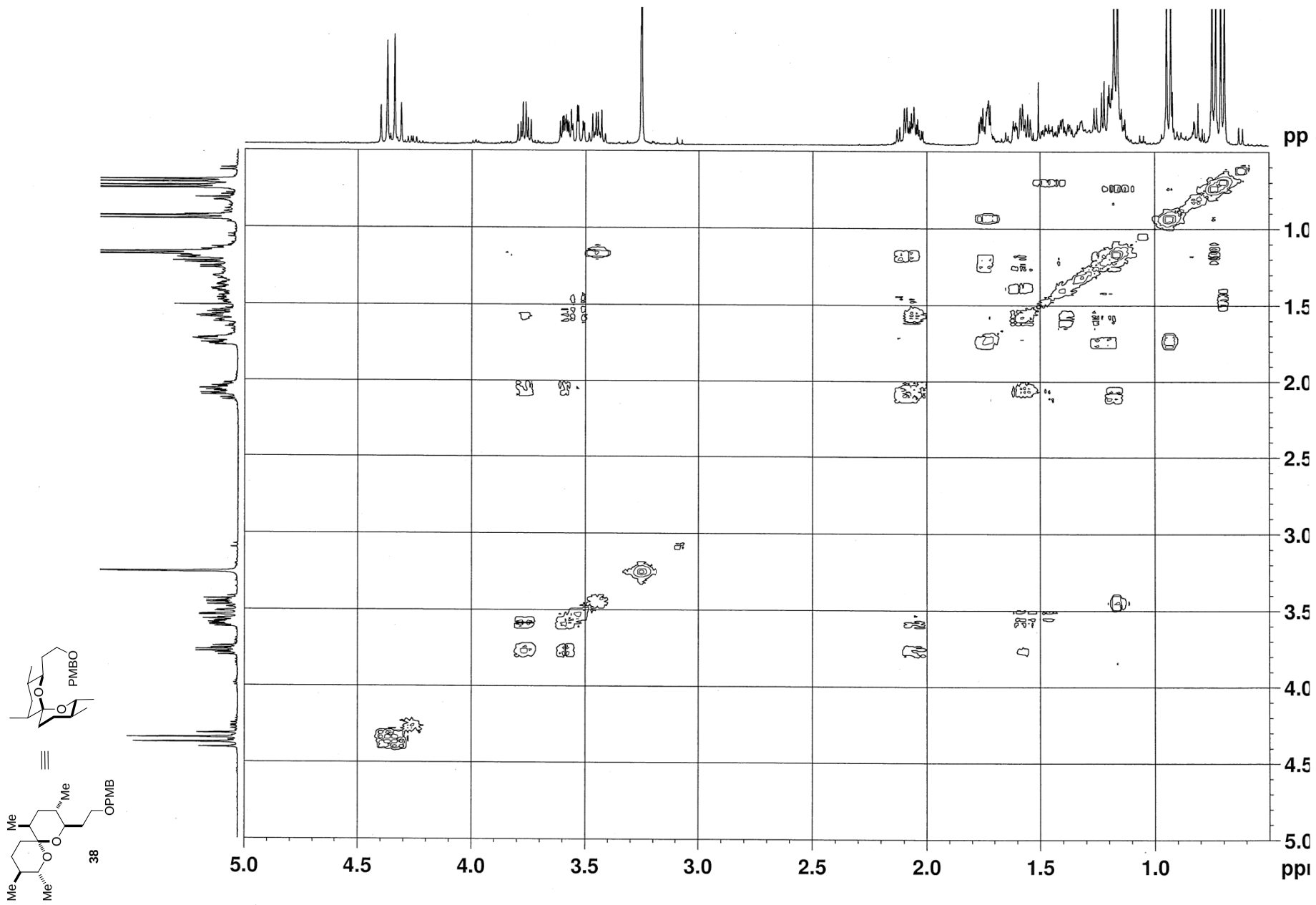
6.79
4.44
4.41
4.38
4.35
3.81
3.80
3.79
3.58
3.29
2.14
2.12
2.11
2.10
2.10
2.09
2.08
1.77
1.76
1.76
1.61
1.27
1.26
1.21
1.20
0.98
0.78
0.77
0.75
0.73
Me
Me
Me
O
O
Me
38
OPMB
O
O
PMBO
2.17
1.90
2.00
0.97
0.88
1.07
1.02
2.85
2.15
1.94
1.95
2.39
1.35
2.75
4.70
3.10
2.83
2.71
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


159.43
131.13
129.52
114.08
97.96
73.09
71.79
71.41
67.35
55.63
36.90
36.57
35.87
33.80
33.56
29.69
28.74
18.42
18.25
15.55
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


PMBO
OPMB
Me
Me
Me
Me
38
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
pp
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0

References:

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[22] The switch was made to a deprotection/ozonolysis protocol due to irreproducibility using the Lemieux-Johnson (OsO_4/$NaIO_4$) system.